Maternal Hemodynamics from Preconception to Delivery: Research and Potential Diagnostic and Therapeutic Implications: Position Statement by Italian Association of Pre-Eclampsia and Italian Society of Perinatal Medicine

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Am J Perinatol

Abstract

Objective The Italian Association of Preeclampsia (AIPE) and the Italian Society of Perinatal Medicine (SIMP) developed clinical questions on maternal hemodynamics state of the art.

Study Design AIPE and SIMP experts were divided in small groups and were invited to propose an overview of the existing literature on specific topics related to the clinical questions proposed, developing, wherever possible, clinical and/or research recommendations based on available evidence, expert opinion, and clinical importance. Draft recommendations with a clinical rationale were submitted to 8th AIPE and SIMP

Keywords
- maternal hemodynamics
- pregnancy
- total peripheral vascular resistance

received
June 19, 2023
accepted after revision
January 28, 2024
accepted manuscript online
February 13, 2024

DOI https://doi.org/10.1055/a-2267-3994.
ISSN 0735-1631.

- fetal growth restriction
- hypertensive disorders of pregnancy
- twin pregnancy
- diabetes
- preterm delivery

Consensus Expert Panel for consideration and approval, with at least 75% agreement required for individual recommendations to be included in the final version.

Results More and more evidence in literature underlines the relationship between maternal and fetal hemodynamics, as well as the relationship between maternal cardiovascular profile and fetal-maternal adverse outcomes such as fetal growth restriction and hypertensive disorders of pregnancy. Experts agreed on proposing a classification of pregnancy hypertension, complications, and cardiovascular states based on three different hemodynamic profiles depending on total peripheral vascular resistance values: hypodynamic ($>$1,300 dynes·s·cm^{-5}), normo-dynamic, and hyperdynamic ($<$800 dynes·s·cm^{-5}) circulation. This differentiation implies different therapeutical strategies, based drugs' characteristics, and maternal cardiovascular profile. Finally, the cardiovascular characteristics of the women may be useful for a rational approach to an appropriate follow-up, due to the increased cardiovascular risk later in life.

Conclusion Although the evidence might not be conclusive, given the lack of large randomized trials, maternal hemodynamics might have great importance in helping clinicians in understanding the pathophysiology and chose a rational treatment of patients with or at risk for pregnancy complications.

Key Points

- Altered maternal hemodynamics is associated to fetal growth restriction.
- Altered maternal hemodynamics is associated to complicated hypertensive disorders of pregnancy.
- Maternal hemodynamics might help choosing a rational treatment during hypertensive disorders.

Maternal hemodynamics and cardiovascular function are gaining more and more importance for the characterization of pregnant women with possible evolution toward fetal and maternal adverse outcomes and/or with established pathological conditions.[1–30] Moreover, women with previous maternal-fetal complications during pregnancy show a higher rate and risk for cardiovascular complications later in life as well as an increased risk of adverse outcomes in further pregnancies.[9,30–34] These risks appear to be related to the cardiovascular profile before, during, or right after pregnancy.

The increasing interest in the hemodynamic changes during pregnancy has led to a new approach in the understanding, screening, diagnosis, and hemodynamic-guided treatment of some of the major complications of pregnancy, in particular hypertensive disorders of pregnancy (HDP) and fetal growth restriction (FGR).[2–5,8,9,11–19,35–37]

Moreover, alongside these widely studied areas, interesting data are emerging regarding other pregnancy diseases such as diabetes and preterm delivery (PTD), as well as a potential role of hemodynamics before pregnancy, in FGR, during tween pregnancy, labor, and delivery with the anesthesiologic implications of hemodynamic profile of the mothers.[38–106]

These new aspects are of interest for obstetricians, cardiologists, internal medicine specialists, and anesthesiologists.

The aims of this consensus are the following:

- To outline the current knowledge regarding maternal hemodynamics, addressing the most common issues related to the possible use of maternal cardiovascular parameters for screening, diagnosis, therapy, and research implications in the various clinical conditions before, during, and after pregnancy.
- To help clinicians, not expert in the field, to understand when hemodynamic parameters can be considered altered, to comprehend the clinical impact of these alterations, and to manage the hemodynamic information for a rational therapeutic use of antihypertensive drugs.

Methods

The maternal hemodynamics experts of the Italian Association of Preeclampsia (AIPE) and of the Italian Society of Perinatal Medicine (SIMP) met to develop clinical questions on the state of the art on maternal hemodynamics. Experts included OBGYN specialists, cardiology/internal medicine, and anesthesiologists and were divided in small groups (2–3 per topic based on their clinical and research experience) and were invited to propose an overview of the existing literature on specific topics related to the clinical questions proposed, developing, wherever possible, clinical and/or research recommendations based on available evidence, expert opinion, and clinical importance.

The topics were:

- Technique for maternal hemodynamic detection: recommendations for a standardization of the detection of the parameters.

- Maternal hemodynamics in FGR:
  - Maternal hemodynamics for the early identification of FGR.
  - Possible treatment for the hypodynamic circulation during early FGR.
- Maternal hemodynamic profiles in chronic hypertension, in the preclinical and clinical phase of gestational hypertension, preeclampsia (PE), and intrauterine growth restriction:
  - Cut-off for the definition of normal dynamics, hypo and hyperdynamic cardiovascular profiles.
  - Possible prediction of maternal-fetal adverse outcome with maternal hemodynamics.
  - Different pharmacological treatment in different hemodynamic profiles.
- Implications of different hemodynamic profiles in preterm labor and labor: possible use of maternal hemodynamics for risk stratifications and recommendations for future research.
- Implications of different hemodynamic profiles during pregnancy in the postpartum follow-up: proposal of a short- and long-term follow-up/intervention based on maternal cardiovascular profile.
- Different maternal hemodynamic profiles during peridural anesthesia in labor: clinical and research implications.
- Different hemodynamic profiles in the preconception: clinical and research implications.

Draft recommendations with a clinical rationale were submitted to the AIPE and SIMP Consensus Expert Panel (H.V., F.M., B.V., G.P.N., S.Z., D.D.Di M., D.F., S.R.G) for consideration and approval, with at least 75% agreement required for individual recommendations to be included in the final version.

Methods for the Evaluation of the Hemodynamics in Pregnancy

One of the most common methods for the assessment of maternal hemodynamics is echocardiography. This method has been used to assess maternal cardiovascular profile in normotensive, chronic, and gestational hypertensive women with or without FGR.[1–25] One of the main parameters that can be assessed is represented by total peripheral vascular resistance (TPVR). This parameter needs a careful assessment of cardiac output (CO) and mean arterial pressure (MAP). Although CO can be detected in several ways with echocardiography (Simpson's method, three-dimensional assessment of left ventricular volumes), in research one of the most used methods is the Doppler evaluation, which has been validated against thermodilution also in severely ill pregnant women.[25] The Doppler method estimates the area under the curve of the aortic flow velocity waveform by pulsed wave interrogation, while two-dimensional (2D) echocardiography is used to determine the area of the aortic valve (►**Fig. 1**). These two parameters allow the calculation of stroke volume (SV), and the detection of the heart rate (HR) gives the possibility to assess CO. ►**Table 1** reports the formulas of the main hemodynamic parameters.

The advantage of echocardiography is the possibility to assess maternal cardiovascular parameters other than maternal hemodynamics, such as right and left ventricular diastolic and systolic function, left ventricular morphology, and speckle tracking studies.

There are many other noninvasive methods to assess maternal hemodynamics such as cardiovascular magnetic resonance imaging, nonimaging continuous-wave Doppler devices, inert-gas rebreathing, bioimpedance, whole-body bioimpedance, bioreactance, noninvasive pulse-contour analysis, and noninvasive pulse-power analysis with continuous noninvasive blood pressure (BP).[1] However, these methods are not interchangeable and need specific reference ranges.[50]

One of the most used devices lately is USCOM (ultrasonic cardiac output monitor), a noninvasive Doppler ultrasonic device for the determination of hemodynamic variables, validated for its use in pregnancy.[26,51] It has several advantages including accuracy, noninvasiveness, speed of performance, fast learning curve, and reproducibility.[27] USCOM utilizes continuous-wave Doppler, with a nonimaging probe, to obtain velocity–time integrals of transaortic blood flow. Initially, the

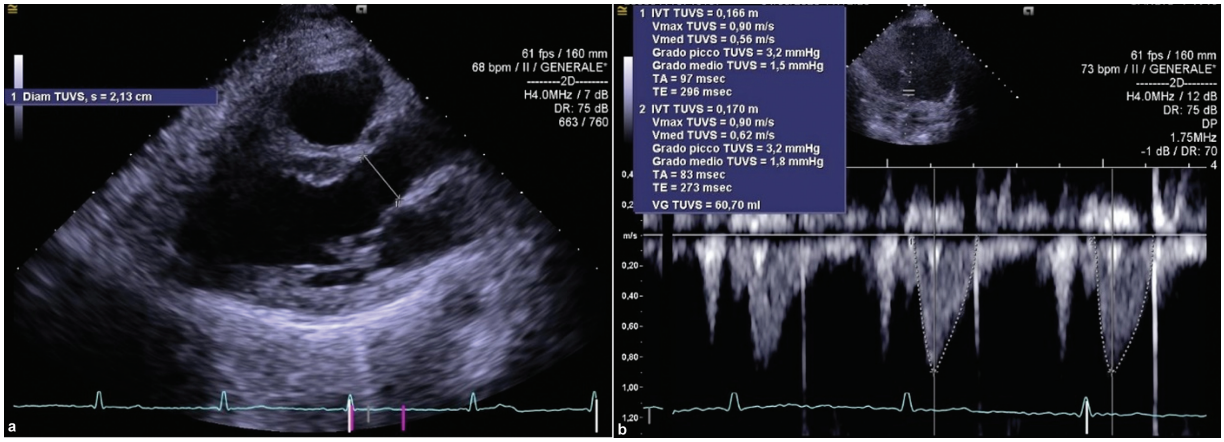

Fig. 1 Detection of cardiac output with the Doppler method. The diameter of the left ventricular outflow tract (LVOT, TUVS in the picture a) to determine the aortic cross-sectional area (CSA); CSA is multiplied by LVOT velocity time integral (LVOT VTI, IVT TUVS in picture b) obtaining SV (VG TUVS in picture b); SV multiplied by the heart rate allows the calculation of the cardiac output. SV, stroke volume.

Table 1 Equations for the main hemodynamic parameters detected with echocardiography and USCOM

Parameter	Formula
MAP	$\mathrm{DBP} + \frac{\mathrm{SBP} - \mathrm{DBP}}{3}$
SV	$\mathrm{LVOT\ VTI} \cdot [(\mathrm{LVOTdiameter}/2)^2 \cdot \pi]$
CO	SV·HR
TPVR	$\frac{\mathrm{MAP}}{\mathrm{CO}} \cdot 80$
INO	*INO* is the sum of potential energy *(PE)* and kinetic energy *(KE)* $\mathrm{PE} = \frac{\Delta P \cdot \Delta V}{\mathrm{TF}}$; $\mathrm{KE} = \frac{1}{2} \cdot mV^2$; $\mathrm{INO} = \mathrm{PE} + \mathrm{KE} = \frac{\mathrm{MAP \cdot SV \cdot 10^{-3}}}{7.5 \cdot \mathrm{TF}} + \frac{1 \cdot \mathrm{SV \cdot D} \cdot V^2 \cdot 10^{-6}}{2 \cdot \mathrm{TF}}$
PKR	$\frac{\mathrm{PE}}{\mathrm{KE}}$ (PE and KE as defined in INO)

Abbreviations: CO, cardiac output; D, density; DBP, diastolic blood pressure; HR, heart rate; INO, Smith Madigan Inotropy Index; LVOT diameter, left ventricular outflow tract diameter (as detected in ►**Fig. 1**); LVOT VTI, left ventricular outflow tract velocity–time integral (as detected with pulsed wave Doppler in ►**Fig. 1**); m, mass; MAP, mean arterial pressure; PKR, potential energy to kinetic energy ratio; SBP, systolic blood pressure; SV, stroke volume; TF, aortic time flow; TPVR, total peripheral vascular resistance; V, aortic velocity; ΔP, pressure gradient; ΔV, volume gradient.

device asks the operator to enter personal, anthropometric data, and BP. Measurements should be performed under standardized conditions, with the patient in the supine position and with the backrest reclined by approximately 30°. The position of the patient during the recordings, given the compression of the uterus on the vena cava during the third trimester, should be similar to that used during the echocardiographic examination (left lateral decubitus). The Doppler probe should be placed perpendicularly to the blood flow out of the heart, at the level of the suprasternal notch. By adjusting the location and angle of the USCOM transducer, the operator optimizes the signal, by following both visual and audible cues from the USCOM display (►**Fig. 2**). The signal recorded is the systolic peak wave coming out of the aorta, preceded by the valve click.[28] Using an internal anthropometric algorithm, USCOM calculates the diameter of the aortic valve based on the patient's height and weight. The device multiplies the velocity–time integral by the aortic root diameter to calculate the SV. By measuring the time interval between each Doppler profile (cardiac cycle), HR can be obtained. Thus, CO can be calculated as follows: CO = SV·HR.[29] Through the calculation of this integral, it is possible to determine over 20 parameters of cardiac function (►**Table 2**).

In fact, in addition to the traditional hemodynamic parameters, the device is able to calculate parameters related to cardiac function such as inotropy index (INO) and potential to kinetic energy ratio (PKR), that is an approximation of arterial impedance. As described later, these data could be helpful to characterize several pregnancy complications.

Recommendation (clinical and research).

For a standardization of the detection of TPVR and other cardiovascular parameters, we propose that maternal hemodynamics is detected during left lateral decubitus independent of the method used. BP should be taken during the examination in the same position. The reason of taking BP in this position and during the examination is that this parameter is necessary to calculate TPVR and therefore the BP

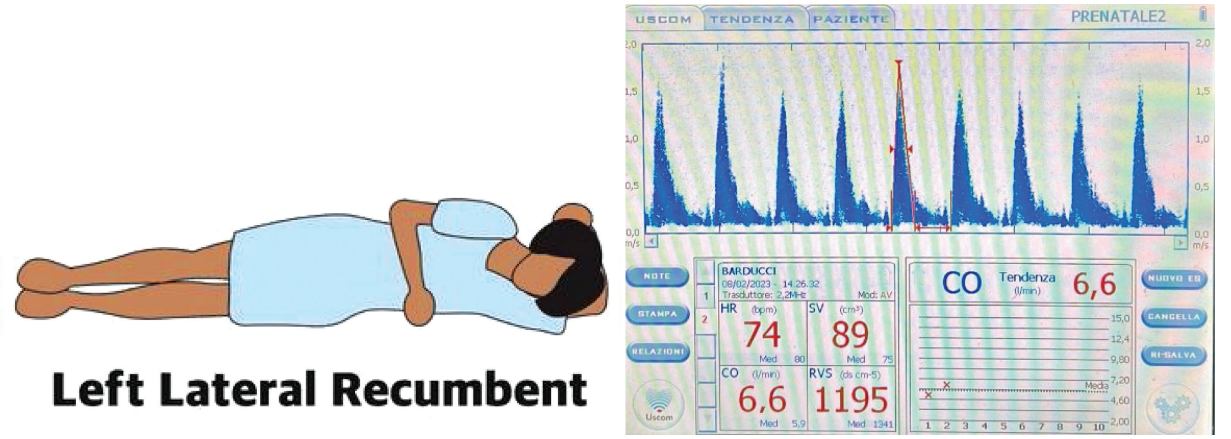

Fig. 2 **The USCOM device.** The picture shows the output of the USCOM device: the probe is placed in the suprasternal notch perpendicular to the aortic blood flow; the Doppler profile of trans-aortic blood flow (upper part of the picture), once entered age, height, and weight of the patient, allows the automatic measurements of CO, HR, SV, and TPVR (lower part of the figure). CO, cardiac output; HR, heart rate; SV, stroke volume; TPVR, total peripheral vascular resistance.

Table 2 Main parameters of cardiac function measured with USCOM device

Measurement	Description
Vpk	*Peak velocity of flow*
VTI	*Velocity time integral*
HR	*Heart rate*
MD	*Minute distance*
ET%	*Ejection time percent*
SV	*Stroke volume*
SVI	*Stroke volume index*
SVV	*Stroke volume variation*
CO	*Cardiac output*
CI	*Cardiac index*
SVR (TPVR)	*Systemic vascular resistance (total peripheral vascular resistance)*
SVRI (TPVRi)	*Systemic vascular resistance index (total peripheral vascular resistance index)*
Pmn	*Mean pressure gradient*
FT	*Flow time*
FTc	*Flow time corrected*
SW	*Stroke work*
CPO	*Cardiac power*
SMII (INO)	*Smith Madigan inotropy index*
PKR	*Potential energy to kinetic energy ratio*

should be related to the SV and CO that are taken during the left lateral decubitus. Moreover, the left lateral recumbent position avoids the possible compression of the gravid uterus on the vena cava during the second and third trimester that might negatively influence the blood pressure and CO.

The Hemodynamic Status of the Woman during the Preconception Phase

Identification of Women at Risk for Complication in Pregnancy

There is evidence that suboptimal pregestational maternal cardiovascular performance affects utero-placental perfusion becoming a cause of placental dysfunction in HDP.[4,65,95]

It is possible to individualize a prepregnancy hemodynamic phenotype associated with complications in pregnancy[96]:

- Reduced plasma volume and decreased vascular distensibility.[91]
- Reduced CO (4.9 vs. 5.8 L/min) and higher TPVR (1,396 vs. 1,156 dyne·s·cm^{-5}).[65]

An altered prepregnancy hemodynamic phenotype in healthy women is associated with the development of HDP and/or FGR.

In chronic hypertension, altered left ventricle (LV) geometry, diastolic dysfunction, and altered TPVR are associated with increased risk of obstetric complications.[4] Increased TPVR (>1,498 dyne·s·cm^{-5}), reduced CO, and concentric ventricle geometry relate to early complications. Low TPVR (<1,048 dyne·s·cm^{-5}), high CO, and eccentric hypertrophy of the LV relate to late complications.[4,97]

Preconceptional hemodynamic assessment identifies chronic hypertension at risk for complications.

The risk of recurrent PE and FGR relates inversely and linearly to preconception plasma volume (8% difference between women who will develop PE and controls).[98]

Lower CO (4.6 vs. 5.3 L/min healthy controls vs. 5.2 L/min nonrecurrence), increased TPVR (1,638 vs. 1,341 vs. 1,383 dyne·s·cm^{-5}), and signs of diastolic dysfunction relate with recurrence risk. Hemodynamic assessment and cardiovascular profile in a healthy woman with previous PE might identify the recurrence risk.[9]

Interesting data on preconception hemodynamics in medically assisted reproduction are also emerging, although these need further confirmations with larger and well-targeted studies.

Possible Interventions before Pregnancy

Pregestational exercise reduces the relative risk of developing PE by 20 to 35%.[99,100]

In previous PE, aerobic exercise, two to three times/week for 12 weeks improves cardiovascular profile,[100] increases plasma volume and venous compliance.[101,102]

Mediterranean diet, intake of micronutrients (folic acid), and other factors (gut microbiome)[15–17] could prevent HDP related to metabolic syndrome.[103–105]

As for prepregnancy therapy in chronic hypertensive patients, preliminary data suggest a role of calcium channel blockers, ACE inhibitors, and angiotensin receptor blockers as protective factors for complications in pregnancy.[4] This protective influence might be due to their action on the

cardiovascular profile and cardiac structure in those patients taking these medications at least 1 year prior to pregnancy, which probably leads a more favorable cardiac geometry and cardiovascular hemodynamics right before pregnancy.[4] These data require further dedicated studies to be confirmed.

As for the cardiovascular profile, few data are available[106] in medically assisted reproduction preliminary but further large studies are needed.

Recommendation (clinical):

In chronic hypertensive fertile women, calcium antagonists and ACE inhibitors/angiotensin receptor blockers might be indicated and may improve cardiovascular profile before pregnancy.

Recommendation (research):

Research in the pregestational phases should be implemented to achieve indications for preventive strategies.

Cardiovascular Changes During Pregnancy

Singleton Pregnancy

Pregnancy can be considered as a "three-compartment model" in which the mother, the fetus, and the placenta interact with each other to maintain a constant equilibrium. In this view, physiological cardiovascular changes have the aim to balance fetal growth and nutrition with maternal survival. These changes start early in the first trimester with a return to the prepregnancy condition about 1 year after delivery.[54]

Pregnancy represents a "cardiovascular stress test" for the mother[55] that, in case of maladaptation of the hemodynamic system, leads to the manifestation of pregnancy complications such as HDP and FGR.[54,55]

Substantially, the result of the physiological cardiovascular adaptation is the creation of a "high flow and low resistance circulation" through an increase of blood volume (in particular of plasma volume with hemodilution), an increase in cardiovascular compliance, and a creation of a hyperdynamic circle. These modifications lead to an adequate perfusion of the uterus which flow during pregnancy increase of about 10 times with respect to the prepregnancy condition.

Arterial BP remains unaffected or demonstrates a tendency toward lower diastolic pressure with a mild reduction of MAP.

The more evident hemodynamic changes are an increase in CO of approximately 30 to 40%, an increase in HR of approximately 20% with a marked fall in TPVR (35–40%).[56] In particular, CO results approximately 40% higher during the third trimester and even higher during uterine contractions in labor. For this reason, these are the major target of maternal cardiovascular assessment, with an increasing role in prevention, diagnosis, and treatment of the main pregnancy complications.[14] The mentioned higher blood volume is associated with an early increase in ventricular wall muscle mass and end-diastolic volume. Moreover, a mild diastolic disfunction is sometimes detected.[57] Alterations in factors related to maternal oxygen transport including oxygen affinity, delivery, and consumption are also detectable.

Twin Pregnancy

Twin pregnancy is traditionally thought to cause an increased strain on the mother's cardiovascular system. Some echocardiographic or impedance cardiography studies have compared maternal cardiac function in uncomplicated twin and singleton pregnancies.[58–61] Despite heterogeneity in design and methodology, most studies found a moderate increase in crude or indexed CO in twins. Peripheral vascular indices are conflictingly reported with TPVR ranging from lower to higher in twin compared with singleton pregnancies.[60–62] Most studies show that subtle forms of left and right ventricular dysfunction are more common in twin than in singleton pregnancies,[58,60–62] suggesting that myocardial remodeling and adaptation are more extreme in twin pregnancies. These variability in data should be interpreted with caution, and the differences in findings may also be gestational age-dependent: some studies adopted a longitudinal design,[58–60] while others pooled together cross-sectional observations in different trimesters[62] or just in mid-pregnancy.[61] Finally, the effect of chorionicity is debated: a recent report[63] showed that women with monochorionic twin pregnancies had a higher PKR and TPVR index in the third trimester, with lower SV and INO versus singleton pregnancies. These differences were not observed in dichorionic (DC) twin pregnancies.[63] Mothers of monochorionic twins may have less extreme cardiovascular adaptation compared with DC, but the magnitude of such difference may be minor.[6,61]

Recommendation (research):

Further studies are needed to go into detail the maternal hemodynamic features on the basis of chorionicity and its influence on maternal fetal complications.

Maternal Hemodynamic Profiles in Different Complications of Pregnancy

Hypertensive Disorders in Pregnancy

To date the classification of hypertension in pregnancy does not take into account maternal cardiovascular profile. Maternal hemodynamics and cardiovascular profile could allow an identification of patients at high risk for complications.[2–5,8,9,11,14–16,21,22,29,35,36,55,64]

The literature allows us to divide pregnant women at risk for complications, normotensive, gestational, and chronic hypertension in pregnancy in three hemodynamic groups:

- High TPVR and low CO (*hypodynamic circulation*).
- Low TPVR and high CO (*hyperdynamic circulation*).
- Normal TPVR and normal CO (*normal-dynamic circulation*).

These cardiovascular profiles may be found also in the preclinical phase of complications and in some cases prior to pregnancy.[4,14,16,65]

Some authors searched for cut-off values of TPVR for the identification of patients at risk for maternal-fetal complications, during normotensive high-risk pregnancies, early mild gestational and chronic hypertension.[4,14,16,66]

The high TPVR and low CO profile appears to be associated to placental PE and FGR, whereas low TPVR and high CO

appears to be related to maternal PE and normal fetal growth.[4,14,16,61,62] The cut-off values for placental PE with maternal echocardiography are more or less set at more than 1,300 to 1,350 dyne·s·cm^{-5}.[14,16,36,66]

Maternal PE often develops when TPVR is less than 800 dyne·s·cm^{-5}.[14]

Normal values of TPVR do not appear to be associated to severe complications.[4,14,16,36,65,66]

It is important to note that the terms *maternal* and *placental* PE refer to the *potential etiologic origin of PE and the different hemodynamic profiles,* but in both forms we can find maternal as well fetal-neonatal unfavorable outcomes.

Recommendation (clinical):

We propose to differentiate the three hemodynamic profiles on the bases the following TPVR values detected with Doppler echocardiography or at the MAP/HR ratio:.

- Hypodynamic circulation TPVR >1,300 dyne·s·cm^{-5}, MAP/HR ratio >1.4.
- Hyperdynamic circulation TPVR <800 dyne·s·cm^{-5}, MAP/HR ratio <1.1.
- Normal dynamic circulation 800 dyne·s·cm^{-5}< TPVR <1,300 dyne·s·cm^{-5}, 1.1 <MAP/HR ratio <1.4.

This assessment would help the clinicians to establish an appropriate medical treatment based on the hemodynamic profile..

Recommendation (research):

Further studies are needed to define the definition of these three profiles with other techniques (USCOM, NICOM, etc.) or other echocardiographic methods (Simpson method)..

Fetal Growth Restriction

The maternal hemodynamic profile in FGR is characterized by low maternal intravascular volume. This profile might be constitutionally determined in normotensive isolated FGR or induced by an insufficient volume expansion in PE with FGR.[67]

FGR implies a condition in which the fetus fails to reach his/hers predetermined growth potential. Similarly to HDP, FGR represents a syndrome, while different causes may underlie this condition. Moreover, there are two main phenotypes, early and late FGR, characterized by different biophysical, clinical, and management profiles. In this paragraph, FGR not linked to genetic, infectious, or congenital abnormality is considered.

Regarding the hemodynamic profile, most data in literature describe early FGR that shares similarities with HDP associated with FGR, consisting in a hypovolemic state with high uterine artery resistance or pulsatility index (PI), low CO, high TPVR, and low plasma volume.[2,5,11,12,15–17,19,29,65,66,68–71] There are some evidence supporting the fact that low plasma volume might be the trigger to altered hemodynamic cascade in early FGR and that this might be at the origin of abnormal placentation observed in early FGR.[65] It seems that preexisting altered cardiovascular profile is present already in the prepregnancy period and that maternal cardiovascular maladaptation is recognizable during the first weeks of pregnancy before placentation.[5,72] These notions open a window toward possible improvement in prediction and prevention. Some authors have already found specific cut-off values of TPVR to predict FGR, in particular the early forms (see sections Cardiovascular Changes during Pregnancy and Maternal Hemodynamic Profiles in Different Complications of Pregnancy, and ►**Table 3**)

Late FGR does not show similar striking cardiovascular maladaptive characteristics as early FGR. However, a subclinical impairment of maternal hemodynamics and cardiac function may be present before pregnancy, becoming evident because of the strain of pregnancy.[73,74] Stott et al[74] described a static pattern with lower CO and SV and higher TPVR in mothers of late FGR compared with pregnancies with neonatal birthweight ≥10th percentile. Indeed, the main issue regarding late FGR is its correct identification/diagnosis, while also other biophysical parameters are blurred in late FGR.

Table 3 Cut-off values of TPVR and week of screening for the identifications of patients at risk for subsequent complications

	TPVR cut-off	Week of screening	Complications predicted
Normotensive nulliparas with bilateral notching of the uterine arteries[62]	*1,400 dynes·s·cm^{-5}* (sensitivity 89%; specificity 94%)[a]	24 weeks' gestation	Composite (GH with preterm delivery, PE, FGR, abruptio placentae, perinatal death)
Early mild gestational hypertension[16]	*1,340 dynes·s·cm^{-5}* (sensitivity 90%; specificity 91%)[a]	27–29 weeks' gestation (before therapy)	Composite (GH with preterm delivery, PE, FGR, abruptio placentae, perinatal death)
Treated chronic hypertension[2]	*1,355 dynes·s·cm^{-5}* (sensitivity 84%, specificity 93%)[a]	24 weeks' gestation	FGR according to Gordijn et al[78]
Normotensive women with suspect FGR[63]	*1,006 dynes·s·cm^{-5}* (sensitivity 92%, specificity 78%)[b] *1222 dynes·s·cm^{-5}* (sensitivity 100%, specificity 96%)[b]	27–29 weeks' gestation	FGR according to Gordijn et al[78] FGR with abnormal umbilical artery flow

Abbreviations: FGR, fetal growth restriction; GH, gestational hypertension; PE, pre-eclampsia.
[a]Maternal echocardiography;
[b]USCOM.

Recommendation (clinical);

A hypodynamic circulation should be taken into account as a risk for the development of early FGR. Different cut-offs should be considered for Doppler echocardiography and USCOM..

Recommendation (research):

Lines of research should clarify the possible constitutional predisposition to low intravascular volume in patients developing isolated FGR..

Further studies are needed to understand the role of maternal hemodynamics in late FGR.

Different techniques should be tested to assess the cut-off of TPVR and other cardiovascular variable as potential predictors of FGR in particular in the late forms.

Diabetes

Limited data on hemodynamics characteristics in pregnancy complicated by diabetes are available. Most of the literature concern the study of hemodynamics in gestational diabetes (GDM). Only one study compared the maternal arterial stiffness in physiological pregnancies and in ones affected by type 2 diabetes (T2DM) and demonstrated that in women with T2DM the arterial stiffness was increased,[38] instead type 1 diabetes seems not to be associated with altered maternal systemic arterial stiffness.[39]

According to the literature, also GDM population has a significant increase in arterial stiffness compared with the physiological pregnancies: this finding could be related to the future development of cardiovascular diseases, in women with previous GDM.[38,40] The mechanisms underlying the increased maternal arterial stiffness in women with GDM are complex: calcifications, alterations in extracellular matrix composition and arterial remodeling due to hyperglycemia, hyperinsulinemia, oxidative stress, chronic inflammation, and endothelial dysfunction may be involved. Maternal arterial stiffness provides an index of vascular status and may reflects a pathophysiological link among insulin resistance, gestational hypertensive disorders, and increased future cardiovascular diseases.

Moreover, these women present higher mean levels of inflammatory biomarkers and TPVR as well as a decreased SV 4 years postpartum, compared with healthy women.[41]

Recently, Khalil et al[42] found that women who will later develop GDM present increased aortic systolic BP and arterial stiffness even in the first trimester of pregnancy before the clinical onset of GDM. Furthermore, GDM patients showed reduced left ventricular diastolic function and global longitudinal systolic strain without differences in ejection fraction at 35 to 36 weeks' gestation compared with controls. These cardiac functional indices improved postpartum in both GDM and controls, but in the GDM group a lower degree of improvement in diastolic indices and systolic strain was demonstrated. Data suggest that women with GDM have alterations in both diastolic and systolic left ventricular function during pregnancy and they are at risk for an accelerated decline in cardiac function long term after delivery.[43]

Mecacci et al confirmed the presence of hemodynamic maladaptation in GDM patients. From a longitudinal analysis of GDM pregnancies, GDM correlated to significantly lower values of CO, SV, and INO, starting from the early third trimester (26–30 weeks) until term, whereas TPVR and PKR are significantly higher.[44]

The abnormal hemodynamic response to pregnancy in GDM women reveals a predisposition to develop cardiovascular diseases later in life, and might help in identifying patients who need a close cardiovascular follow-up.

Recommendation (research):

Further studies are needed to validate this hypothesis and to verify if these changes in hemodynamic parameters among GDM women are already present in pregestational age, and connected with gestational outcome, in particular PE and long-term cardiovascular disease.

Maternal Hemodynamics as a Screening for Complications in Pregnancy: Hypertensive Disorders in Pregnancy and Fetal Growth Restriction

To date, no tests in the first trimester can reliably predict all cases of HDP; however, a combination of maternal risk factors, BP values, placental growth factor (PlGF) dosage, and uterine artery Doppler velocimetry can screen pregnant women who may benefit from Aspirin 150 mg/day to prevent the occurrence of early and, to a lesser extent, preterm PE. Moreover, no test including maternal hemodynamic parameters to predict, from the first trimester, hypertensive complication, or FGR exists yet.

Some data suggest that maternal hemodynamic and impedance, in the first trimester of pregnancy, could add relevant information to sort out those women at higher risk of FGR and early HDP.[75–78] This phenotype is characterized by low CO, probably preexisting to conception, and high TPVR, and represents, as explained before, the so-called placenta-related HDP. This kind of HDP is different from the most common one associated to an intravascular volume overload hypertension, defined as maternal HDP. As such, the fundamental physiologic definition of BP as the product of CO and TPVR comes back into the spotlights: hypertension is the result of either increased vascular resistance, a high intravascular volume, or both. These pathophysiologic concepts could be exploited for screening different phenotypes when the traditional multivariable screening could be patient-tailored by adding maternal hemodynamic and not only peripheral BP, and maternal body water and not only body mass index. The inclusion of these new parameters in the classic PE prediction algorithm appears to be promising to better differentiate and predict the different phenotypes. In fact, in the second trimester of pregnancy, hemodynamic parameters seem to help discriminating patients at risk for PE and/or FGR.[2,16,66,68] Moreover,

hemodynamics parameters in case of isolated FGR could help the physician to predict the development of associated HDP. Some studies have identified cut-off values of TPVR as risk factors for the development of complications in pregnancy, in particular in case of high-risk pregnancy with bilateral notching of the uterine artery at 24 weeks' gestation,[66] early gestational hypertension,[16] treated chronic hypertension,[2] and patients at risk for isolated FGR,[68] as diagnosed according to Gordijn et al.[78] ►Table 3 reports the cut-off values, the method used to find the cut-offs, and the week of the screening.

Other techniques for maternal hemodynamic detection have shown promising results for the prediction of HDP such as bioimpedance, impedance cardiography, and ECG-Doppler ultrasound.[79,80]

Recommendation (clinical):

The different phenotypes of hypertension are associated to a bimodal hemodynamic pattern of HDP, which bears clinical implications as for the preventive use of immunomodulation thorough low-dose aspirin, and eventually low-molecular-weight heparin (for which the use is still debated and remains to be fully proven) in cases of low CO, low PlGF, and high uterine Doppler velocimetry, whereas a proactive lifestyle intervention could be useful in women with metabolic syndrome, high body water, normal-high CO, normal PlGF, normal uterine arteries.

Risk Stratification of the Severe Complications in Pregnancy

Several studies have demonstrated that BP values are poor prognostic indicators of an adverse maternal and neonatal outcome in women with HDP or at risk for complications.[2–5,8,9,11,14–16,21,22,29,35,36,55] Maternal cardiac assessment at different stages of pregnancy and in different sets of women might be considered as a tool to predict an adverse pregnancy outcome.[2,16,66,68]

Maternal echocardiography could help in identifying women with early mild gestational hypertension who subsequently develop maternal and fetal complications: TPVR $>1{,}300$ dyne·s·cm^{-5} and the presence of a concentric geometry of the LV were found to be predictors of subsequent pregnancy complication.[16]

A recent study on mild preeclamptic women found that both the maternal cardiac findings and the uterine artery Doppler velocimetry are significantly different at the time of the diagnosis in patients remaining stable compared with those progressing toward a severe disease and organ dysfunction.[81] In particular, women with mild PE with high maternal TPVR and uterine artery PI show a more profound placental impairment, predicting the likelihood of progression toward a severe condition.[81]

Furthermore, a correlation between maternal hemodynamics parameters and the perinatal outcome has also been demonstrated among normotensive pregnant women with small for gestational age fetus (estimated fetal weight $<$10th centile) in the third trimester.[71] More specifically, it has been found that a lower maternal CO at the sonographic diagnosis of fetal smallness is more common when the established criteria of FGR are fulfilled and is a significant independent predictor of the length of neonatal hospitalization.[71]

The correlation between an hypodynamic maternal cardiovascular profile and FGR[70] has led to the search for hemodynamic parameters predicting this condition.[2,68] In chronic hypertensive patients, high TPVR assessed through echocardiography at 24 weeks' gestation may predict the development of FGR (►Table 3).[2] As well, normotensive patients with a suspect of FGR might be correctly identified with TPVR as assessed by USCOM (►Table 3).[68]

Recommendation (clinical):

Based on the correlation between the severity of the maternal cardiac impairment and the occurrence of adverse maternal and neonatal outcome, we envisage that maternal hemodynamic assessment by means of echocardiography or a noninvasive device, whenever available, should be considered.

Hemodynamic Guided Treatment in Pregnancy Complicated by Early Fetal Growth Restriction

As previously described, maternal cardiovascular profile appears to be altered when pregnancy is complicated by FGR and is typically characterized by a hypodynamic circulation probably associated to a reduced venous capacitance and hypovolemia.[17,19,73,82] The therapeutic approach should therefore take into account these hemodynamic profiles, using drugs capable to act on both the arterial and venous systems. Nitric oxide (NO) donors appear to be promising, since they reduce the vascular resistance, modify the venous system capacitance, and increase the HR and contractility of the myocardium. Transdermal glyceryl trinitrate patches that release NO are effective in increasing the availability of NO at the level of the tissues, which leads to vasodilatation.[12,15] The increase in plasma volume with oral or intravenous hydration adds to the pharmacologic effect, potentially restoring SV and CO.[12,15] These effects on the maternal side might reflect on the fetal vascular system,[83] which is interconnected with the maternal one.[70] Some authors have demonstrated promising results with this approach in gestational hypertension complicated by severe FGR with altered umbilical artery Doppler velocimetry[15] and in gestational hypertension with a hypodynamic circulation, leading to a reduction of fetal complications by 50% compared with patients treated with antihypertensive drugs not associated to NO donors and increased fluid intake.[12] The clinical protocol consists in the addition of NO donor patches 5 to 10 mg 12 h/day and oral hydration in patients with a hypodynamic circulation and/or FGR.[12,15] To avoid tolerance, it is important to administrate NO donors with an on-off strategy. If the patient is already treated with antihypertensive drugs, this pharmacological approach is added on top of the treatment.[12] Moreover, a reduction of

physical activity (housekeeping, abstention from work) might help in reducing TPVR.[7]

Recommendation (clinical):

In case of hypodynamic circulation (high TPVR low CO) and FGR, NO donors (patches up to 10 mg/12 hours per day) and an increase in oral fluids (2.5–3 L per day) may be considered. In this case, maternal hemodynamics should be evaluated again within 7–10 days to verify the effects of the treatment and for therapeutical adjustment if necessary.

Recommendation (research):

The effect of NO donors and increase in oral fluids have to be assessed in chronic hypertension as well as in the preclinical stages of FGR. Research is needed in this field with well-designed randomized trials.

Hemodynamic-Guided Treatment in Hypertensive Disorders of Pregnancy

To date, medical treatment of HDP is still based on BP values. Some authors have tried to tailor therapy on the basis of maternal hemodynamics obtaining a reduction of maternal and fetal complications.[12,35,36] Stott et al[84] in a previous report evidenced how TPVR detected through bioreactance technology (NICOM—Non-Invasive Cardiac Output Monitor), could identify hypertensive pregnant patients who are unlikely to respond to labetalol therapy, therefore needing vasodilatory therapy. When choosing a drug treatment, HR at least should be taken into account (►Table 4).[35] Whenever possible MAP and CO, as well as TPVR, should be assessed before and/or during antihypertensive treatment.[35] TPVR $>1{,}300$ dyne·s·cm^{-5} as well as the ratio MAP/HR >1.4 identify a hypodynamic circulation, whereas TPVR <800 dyne·s·cm^{-5} or MAP/HR <1.1 are signs of a hyperdynamic circulation with different types of related complications.[12,35–37] With this method, Mulder et al[36] demonstrated in a randomized controlled trial that a tailored treatment based on MAP/HR might halve the risk of recurrent PE. In a previous report, Vasapollo et al[12] showed that treatment of hypodynamic gestational hypertension with NO donors and increased oral fluid intake added to nifedipine might reduce overall and fetal neonatal complications correcting the hemodynamic profile of the mothers.

To choose the correct antihypertensive therapy in pregnancy, we propose to apply three rules:

- Evaluation of cardiovascular profile on the basis of the main hemodynamic parameters: at least maternal HR and MAP, wherever possible CO and TPVR.
- Choose the appropriate treatment on the basis of hemodynamic results, considering the pharmacological effects of the main antihypertensive drugs, extensively used in pregnancy.
- Verify the cardiovascular response to treatment after a time interval of 7 to 14 days, performing, whenever possible a hemodynamic assessment.

The tailored treatment based on cardiovascular parameters would avoid irrational pharmacological approach preventing or mitigating PE and other severe complications.[12,36]

►Table 4 proposes a possible guide to identify the correct treatment according to maternal cardiovascular features.

Recommendation (clinical):

Increasing evidence suggests that pharmacological treatment of HDP should be targeted on maternal hemodynamics.

- Hypodynamic circulation requires calcium antagonists (eventually adding NO donors and increased oral fluid intake).
- Hyperdynamic circulation may be better treated with β-blockers such as labetalol.
- Normal dynamic HDP can be treated with α-methyl-dopa.

Table 4 Maternal hemodynamic profile and proposed pharmacological approach

Parameter	Hyperdynamic circulation	Hypodynamic circulation
Heart rate[35]	>90 beats/min Alpha and beta blockers (alpha methyldopa, labetalol), calcium channel blockers (amlodipine, diltiazem)	<70 beats/min Calcium channel blockers (nifedipine), NO donors + oral fluids
Cardiac output[35]	>8 L/min Alpha and beta blockers (alpha methyldopa, labetalol)	<5 L/min Calcium channel blockers (nifedipine), NO donors + fluids
Total peripheral vascular resistance[35]	<800 dynes.s.cm^{-5} Alpha and beta blockers (alpha methyldopa, labetalol)	>1,300 dynes.s.cm^{-5} Calcium channel blockers (nifedipine), NO donors + fluids
Mean arterial pressure/ Heart rate[36]	<1.1 Labetalol	>1.4 Nifedipine, NO donors + oral fluids

Source: Adapted from Vasapollo et al[35] and Mulder et al.[36]

Hemodynamics in Preterm Delivery and Labor

PTD is a multifactorial complication of pregnancy, based on several pathophysiological mechanisms that are currently mostly unknown. It is an important lifetime risk factor for cardiovascular disease in women.[33] Maternal hemodynamics identified two different cardiovascular phenotypes in pregnancy at risk of PTD, according to the presence or absence of preterm premature rupture of the membrane (pPROM). PTD is more common in patients with high TPVR, low CO, low inotropism (INO), and hypodynamic circulation.[45] This suboptimal cardiovascular adaptation might result from a vascular reaction caused by a subtle inflammatory state and could be the cause of maturational defects of placental villi described in these patients.[45] On the contrary, the hemodynamic profile of patients with pPROM is characterized by a hyperdynamic circulation, more and more pronounced in patients developing more unfavorable outcomes.[85] This hyperdynamic circulation is correlated to inflammation derived from higher prevalence of choriodecidual infection. ►Table 5 shows the main differences between PDT with and without pPROM.

Modern technologies allow a rapid, accurate, and noninvasive assessment of maternal hemodynamics during labor.[51] Labor is a stress test for cardiovascular system which must guarantee blood supply to the fetal-placental unit. In particular, during the second stage, uterine contractions and maternal pushing seem to reduce the CO and then the blood supply to the uterus. Moreover, even though conflicting results about different drugs have been published, it must be considered that analgesia during labor may have direct or indirect effects on maternal hemodynamics. For this reason, an optimal cardiovascular function seems to be crucial for fetal well-being during labor.

Maternal hemodynamic assessment at the end of pregnancy, or during the labor, could identify specific alterations that increase the risk for intrapartum fetal demise in patients with low-risk or high-risk pregnancies.[46] In particular, low CO and high TPVR appear to be associated with higher risk of fetal distress or maternal complications.[46]

For this reason, maternal hemodynamic assessment could be useful at the end of pregnancy to identify high-risk pregnancy.

Recommendation (research):

Multicenter studies have to clarify the cut-off values for the risk of possible adverse outcomes in labor.

Anesthesiological Implications of Different Maternal Hemodynamic Profiles

The administration of epidural anesthesia can have different effects on fetal HR (FHR) and cardiotocography profile depending on the hemodynamic status of the mother at the beginning of labor. A recent study on normotensive healthy women observed that a high CO (low TPVR) was associated to a low number of decelerations at CTG, 1 hour after the epidural bolus,[48] while the short-term variation was lower in the group with low CO (high TPVR).[48] This is in line with a previous report on combined spinal-epidural anesthesia, highlighting that TPVR $>1{,}200\,\text{dyne}\cdot\text{s}\cdot\text{cm}^{-5}$ as obtained with USCOM is associated to an increased incidence of patients with CTG abnormalities.[49] In particular, patients with elevated TPVR who are not able to increase SV and CO after combined spinal-epidural anesthesia appear to be at greater risk of FHR anomalies.[49] These aspects of maternal hemodynamics might have implications on fetal wellbeing when administering spinal epidural anesthesia in the different types of HDP, with different cardiovascular profiles (hyper- or hypo-dynamic). The most severe forms of PE include severe hypertension and signs/symptoms of end-organ injury. The better understanding of pathophysiology and the emergence of minimally invasive techniques to evaluate hemodynamics have the potential for new forms of treatment, with a multidisciplinary team approach essential to improve maternal and fetal outcomes.

From an anesthesiological standpoint, neuraxial analgesia and anesthesia are beneficial for both mother and baby, the former improving placental gas exchange, the latter avoiding a general anesthesia with the risk of a "failed-airway" and consequent maternal complications; if required, intravenous medications (e.g., remifentanil, esmolol) are recommended to attenuate the stress response to laryngoscopy and intubation. Because of the reduced colloid osmotic pressure and the increased pulmonary capillary permeability, intravascular volume management should be restrictive ($\leq$ 80 mL/h) to limit the risk of pulmonary edema. Ideally, it should be based on markers of end-organ perfusion (e.g., urine output, pH,

Table 5 Schematics of the differences between spontaneous preterm delivery and preterm delivery due to pPROM

	Preterm delivery	pPROM
Type of inflammation	Subtle inflammation	Evident inflammation/infection
TPVR	↑	↓
CO	↓	↑
INO	↓	=
PKR	↑	↓

Abbreviations: CO, cardiac output; INO, Smith Madigan inotropy index; PKR, potential energy to kinetic energy ratio; TPVR, total peripheral vascular resistance.

and lactate), lung ultrasonography, and on hemodynamic monitoring.

Moreover, patients with severe PE have greater endogenous vasoactive mediators and are more sensitive to exogenous vasopressors indicating that require less vasopressors than normotensive pregnant patients.[86]

Recommendation (research):

Preliminary data suggest a role of maternal hemodynamics for a successful and uneventful management of anesthesia during labor. Research should be implemented in this field to assess the usefulness and practical indications for anesthesiologists, obstetricians, and neonatologists.

Follow-Up after Delivery on the Basis of the Hemodynamic Profile during Pregnancy

A cardiovascular and metabolic follow-up of patients who develop pregnancy complications should be always scheduled with a visit at 1, 6, and 12 months postpartum, and thereafter with an annual check. In fact, patients with different complications of pregnancy have been found to have an increased risk of cardiovascular diseases and diabetes mellitus later in life,[31,32,34,87,88] as well as an increased risk of complications in future pregnancies.[9] In particular FGR, HDP, and PTD represent a potent cardiovascular risk for future life.[31,87] The approach to these patients during follow-up might change according to the complications developed during pregnancy and the associated hemodynamic profile. Maternal HDP, for example, is often associated to maternal modifiable risk factors such as obesity. Obesity is associated with a hemodynamic overload,[45,89] due to an increased SV and an increase in HR,[90–92] causing higher CO.[93,94] The correction of maternal life style can reduce the subsequent risk of cardiovascular diseases later in life.

Placental HDP, FGR, and PTD appear to be associated to a hypodynamic circulation and body mass index is usually normal.[2,4,9,14,17,18,45] This challenging situation requires a careful evaluation of the modifiable and unmodifiable risk factor, since the maternal phenotype might be misleading.

Recommendation (clinical):

We suggest that women with complications in pregnancy and with hemodynamic abnormalities should be subjected to a short- and long-term cardiovascular follow-up. Particular attention should be placed in those patients with adverse outcome of pregnancy related to hemodynamic alterations without evidence of modifiable risk factors. In these patients a postpartum cardiovascular follow-up should be strongly advised.

Conclusion

Maternal hemodynamics and cardiac function are becoming more and more important for the identification of the maternal cardiovascular profile before, during, and after pregnancy.

The identification of a deviation from a normo-dynamic profile (either hypodynamic or hyperdynamic), normal cardiac function, and structure may precede maternal and fetal adverse outcomes. Moreover, the correct classification of the cardiovascular profiles could be useful for a rational pharmacological approach in patients with HDP/FGR. Finally, the cardiovascular characteristics of the women may be useful for a rational approach to an appropriate follow-up, due to the increased cardiovascular risk later in life.

Funding
None.

Conflict of Interest
None declared.

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