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Assessment of arterial function in pregnancy: recommendations of the International Working Group on Maternal Hemodynamics

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ABSTRACT

There is strong evidence supporting the role of maternal arterial dysfunction in pregnancy-specific disorders such as pre-eclampsia and intrauterine growth restriction. As more work is focused towards this field, it is important that methods and interpretation of arterial function assessment are applied appropriately. Here, we summarize techniques and devices commonly used in maternal health studies, with consideration of their technical application in pregnant cohorts. Copyright © 2017 ISUOG. Published by John Wiley & Sons Ltd.

INTRODUCTION

Arterial function is recognized as an important 'risk marker' in evaluating cardiovascular disease. Several parameters exist with which to assess localized and global arterial function in both the clinical and research setting. These are summarized in a consensus report of the European Network for Non-invasive Investigation of Large Arteries[1]; however, specific guidance for their use in pregnant cohorts is lacking. Here, we outline suitable techniques and devices for assessment of arterial function in pregnancy and for the interpretation of results. We also briefly summarize key studies of arterial function in normal pregnancies and those with adverse outcome.

THE ARTERIAL SYSTEM

The arterial tree branches from the aorta, terminating in the smallest arterioles, from which capillaries arise. Due to the pulsatile nature of cardiac ejection, blood pressure and flow oscillate throughout the arterial tree.

Elasticity of the aorta, which is a large elastin-containing vessel, plays an important role in buffering oscillatory changes in blood pressure. Local adjustments to vascular tone in the smooth muscle, that predominates in smaller arteries and arterioles, also help to regulate arterial blood flow. Common indices of large-artery elasticity and vascular-tone regulation include arterial stiffness, arterial-wave reflection and endothelial function.

ARTERIAL STIFFNESS

Large arteries are important in buffering cyclical changes in blood pressure by reducing peak pressure, maintaining diastolic pressure and smoothing blood flow. With increased arterial stiffening, which occurs with age, genetic predisposition (e.g. with genes involved in the differentiation of vascular smooth-muscle cells)[2] and pathological processes such as atherosclerosis, there is an overall increase in pulse pressure, resulting in isolated systolic hypertension. The repeated cyclical stress of high pulse pressure propagates a cycle of further arterial stiffening through fatigue fracture of the elastic elements within the arterial wall.

Arterial stiffness can be quantified by the pulse-wave velocity (PWV), which is a measure of the velocity of blood flow in the aorta. The velocity of the pressure wave is inversely related to vessel elasticity and compliance. As arteries stiffen, the transmission velocity, commonly expressed as PWV, increases. PWV also increases as the

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pressure wave travels from the aorta to the periphery, indicating that vascular compliance is lower in the distal parts of the arterial tree.

Aortic PWV is considered the 'gold standard' measurement of arterial stiffness, as the thoracic and abdominal aorta makes the largest contribution to arterial buffering actions, and aortic PWV is an established independent predictor of outcome[1]. Arterial stiffness, assessed by measuring aortic PWV, is an independent predictor of cardiovascular mortality and morbidity in hypertension, Type-2 diabetes and end-stage renal failure[1]. In a meta-analysis of over 17 000 participants, aortic PWV reclassified risk and improved model fit for future cardiovascular events, even after accounting for standard risk factors[3].

However, the carotid-femoral pathway is commonly used as a pragmatic surrogate for the aortic system as it covers the region that exhibits the greatest age-related stiffening[4], and both arteries are superficial and easy to palpate. The 2011 European Society of Hypertension guidelines suggest that, in arterial hypertension, carotid-femoral PWV over 10 m/s relates to subclinical organ damage and cardiovascular events[5]. There are no reported normal limits for PWV in pregnancy, although <10 m/s is within the range for healthy non-pregnant women[6]. PWV has been reported to increase significantly with maternal weight and age, but not with parity or smoking status[7].

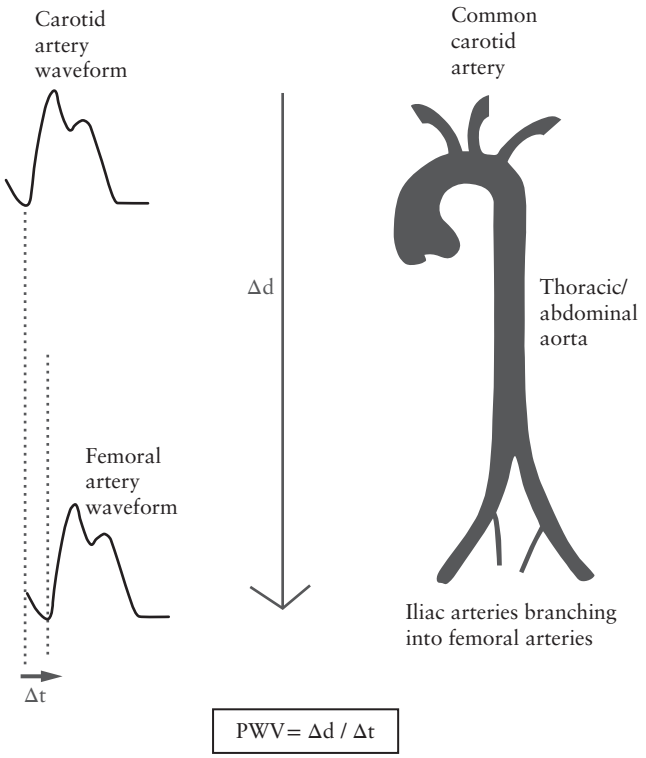

Figure 1 'Foot-to-foot' measurement of carotid-femoral pulse-wave velocity (PWV).

PWV measurement techniques and devices

PWV is calculated by measuring the transit time (Δt) taken for a pressure pulse to travel between two set points; for carotid-femoral PWV, it is measured from the common carotid artery to the ipsilateral femoral artery. Although direct carotid-femoral measurements are preferred, this may not always be feasible. Several non-invasive devices derive the distance (Δd) covered by the pulse wave approximated to surface distance between two marked sites. PWV is calculated as: Δd (in meters) / Δt (in seconds). Figure 1 illustrates the foot-to-foot measurement of carotid-femoral PWV (with 'foot' of pulse wave defined at the end of diastole).

Measurement of distance is relatively simple with the use of a ruler or measuring tape, although the site (e.g. measuring the carotid wave at or above the sternal notch) should always be standardized for all tests within a cohort. In pregnancy, it is advisable to use metal calipers rather than tape measure due to the distortion of linear distance measurements by the shape of the pregnant uterus.

To measure time delay between pressure waveforms (Δt), there is a variety of devices utilizing computerized oscillometry[6], applanation tonometry[8], Doppler[9] or mechanotransducers[10]. There is no consensus regarding which method or device is most valid[11,12], and most, due to their non-invasive nature, are suitable for use in pregnancy. Most devices have been validated against invasive testing in non-pregnant cohorts, but not in pregnancy[13–15]. Incremental increases in distending pressure, as represented by mean arterial pressure (MAP), increase PWV; therefore, MAP levels should be taken into account when comparing groups[16]. The effect of heart rate is less clear but this may also be a confounding factor[16].

The Complior System® (Alam Medical), based on the piezoelectric principle, uses skin mechanotransducers to detect simultaneously in two different arteries or at two different sites waveforms which can be visualized onscreen by the operator. Once waveforms of sufficient quality are recorded, the Δt between the pressure waveforms at each site is calculated using a correlation algorithm on the initial pulse rise to just after true pulse peak, and PWV is calculated.

Pressure waves can also be recorded sequentially at different sites, and Δt calculated from a simultaneous electrocardiographic (ECG) recording. The SphygmoCor® system (AtCor Medical), a device with moderate reproducibility[17], uses high-fidelity applanation tonometry to obtain successive proximal and distal pulses a short time apart. Δt is then determined as the time difference of the ECG R-wave in relation to the distal and proximal pulses. As the measurements are a short time apart, changes in heart rate variability have minimal effect on Δt.

The Arteriograph® (Tensiomed) and Vicorder® (Skidmore Medical Ltd) devices use an oscillometric distension technique to obtain PWV. The Vicorder has not been validated against invasive testing for pulse-wave analysis; however, it has been validated against the SphygmoCor and shows good agreement of aortic PWV values, albeit with an inherent bias towards lower Vicorder aortic PWV values at higher values of SphygmoCor aortic PWV[18]. When using the Vicorder, a pad that inflates over several

centimeters is placed around the patient's neck, and a cuff is placed around the patient's upper right thigh. Both carotid and femoral cuffs are inflated to 65 mmHg and the corresponding oscillometric signal from each cuff is obtained in real time. Once the operator is satisfied with the waveform quality, the test is terminated and an algorithm of the two waveforms is analyzed to produce Δt.

The Arteriograph is based on plethysmography and registers pulsatile pressure changes in an artery. Typically, upper-arm blood pressure is first measured using a cuff, which is inflated to at least 35 mmHg above systolic pressure, and brachial artery pressure fluctuations are analyzed. The difference in time between the beginning of the first wave and the beginning of the second (reflected) wave is related to a measured distance from the jugular notch to the pubic symphysis, allowing calculation of the PWV.

ARTERIAL WAVE REFLECTION

Another surrogate measure of arterial stiffness is the arterial pressure waveform, which is a composite of a forward-traveling wave generated by left ventricular ejection, and a backward-traveling reflected wave arising from sites of impedance mismatch, such as arterial taper and major arterial bifurcations. The change in impedance is thought to generate wave reflections, similar to the effect when a stone is dropped into a small pond and waves hitting the pond edge are reflected back towards the center, that summate to form a single effective reflected wave that flows back into the ascending aorta early in the cardiac cycle.

As arterial compliance decreases, the speed of travel of the wave increases. This means that the reflected wave superimposes on the advancing pulse wave at an earlier time, increasing the amplitude of the forward wave; in other words, augmenting the systolic pressure wave. This can be quantified using the augmentation index (AIx), which is the ratio of the pressure difference (amplitude difference between the start of a first wave, P1, and the start of a second reflected wave, P2) in relation to the pulse pressure, usually expressed as a percentage (Figure 2). While PWV reflects aortic stiffness, AIx is to some extent determined by endothelial dysfunction and arterial resistance, and is thought to be a more sensitive early marker of arterial stiffness[19]. Central AIx has been shown to be an independent predictor of all-cause mortality in patients with end-stage renal disease or hypertension[20,21]. AIx increases linearly with age until 50–60 years, when it plateaus[8,22].

AIx measurement and devices

AIx should be analyzed in the ascending aorta, which most accurately represents the ventricular afterload imposed by central large arterial walls. However, it is difficult to obtain direct measurements from central arteries; therefore, AIx is commonly estimated from either the radial or the brachial artery waveform. Using a validated

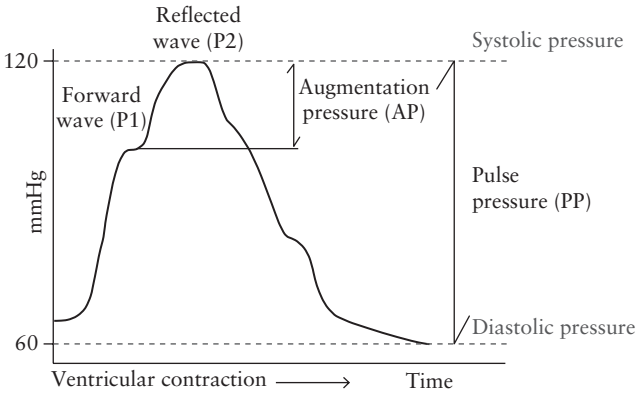

Figure 2 The arterial waveform complex.

transfer function, an aortic pressure waveform is then calculated from the peripheral arterial waveform. AIx increases with MAP and is inversely related to heart rate and body height, so these variables should be taken into account when interpreting results. Commonly, AIx is standardized to a heart rate of 75 bpm (AIx-75). In pregnancy, maternal ethnicity, smoking, parity, body mass index and mean uterine artery pulsatility index were found not to be significant predictors of AIx-75[23].

The most widely used approach is to perform tonometry in the upper limb, usually in the radial artery, with a high-fidelity probe such as the Millar strain gauge transducer (SPT-301, Millar Instruments, Sydney, Australia). The pressure waveform is then transformed using a transfer function[17] (SphygmoCor) to calculate the aortic AIx. Alternatively, carotid tonometry can be used. For this, a transfer function is not necessary as the arterial sites are quite close and the observed waveforms are similar. However, carotid tonometry requires more technical expertise, so there is more room for operator error, especially in obese patients in whom the carotid artery may be more difficult to palpate. While AIx is a relative measurement and can be calculated without calibration, its components (central pulse, heart rate, augmentation and systolic blood pressure) are absolute values and require calibration[1].

Oscillometric devices such as the Vicorder and Arteriograph (as described above) can also be used to analyze pressure waveforms. Brachial artery waveforms are obtained using a fluid distension technique via cuff inflation on the upper arm. Similar to tonometry, these waveforms are then transformed by a transfer function to produce aortic AIx. There have been no comparative studies between Vicorder and tonometry in pregnant women. In a non-pregnant cohort of chronic obstructive pulmonary disease patients, Vicorder AIx measurements correlated significantly with SphygmoCor ones; however, the limits of agreement were only −10.42 to 9.02%, with a coefficient of reproducibility of 27.9%[24]. Vicorder values were lower but there was satisfactory agreement[24].

The Arteriograph obtains AIx by calculating the pressure difference (amplitude difference between the start of a first wave, P1, and the start of a second reflected

Table 1 Devices for measuring arterial stiffness (pulse-wave velocity (PWV) and augmentation index (AIx))

Technique/Device	*Advantages*	*Disadvantages*
Mechanotransducer Complior® (Alam Medical, Pantin, France)	Widely used in first few epidemiological studies that demonstrated predictive value of PWV in CVDs Simultaneous recording of central and peripheral signal Portable device	Errors associated with distance estimation signal
Oscillometric fluid distension Arteriograph® (Tensiomed, Budapest, Hungary) Vicorder® (Skidmore Medical Ltd, Bristol, UK)	Affordable Non-invasive Good intraobserver variability Can obtain AIx and central systolic BP	Vicorder not yet validated against invasive techniques for arterial function testing
Tonometry SphygmoCor® (AtCor Medical, Sydney, Australia)	Used in many large observational studies linking arterial function to cardiovascular events	Expensive Measured distance is an estimation of true distance and largely depends on body habitus
Omron HEM-9000AI® (Omron Healthcare, Kyoto, Japan)	Similar to SphygmoCor and can obtain AIx and central systolic BP Portable	Cannot obtain carotid-femoral PWV
Ultrasound	Can analyze waveforms simultaneously or separately using ECG synchronization	Requires extensive training User-dependent variability
Photoplethysmography PulseTrace PCA 2 and PulseTracePWV® (Micro Medical, Bournemouth, UK)	More suitable for use in overweight populations	Only gives information on waveforms at peripheral body sites; information on central arterial waveforms less reliable Inferior quality of waveform obtained from finger probe
Cardioankle vascular index VaSera System® (Fukuda Denshi, Tokyo, Japan)	Records distensibility of whole aortic-iliac, femoral-tibial system	Needs further validation process in comparison to carotid-femoral PWV

All devices tabulated are non-invasive, and none has been validated against invasive techniques in pregnancy. BP, blood pressure; CVD, cardiovascular disorder; ECG, electrocardiograph.

wave, P2) in relation to the pulse pressure. The brachial artery waveform readings allow AIx calculation as: AIx (%) = ((P2 − P1)/PP) × 100, where PP is pulse pressure, and thus provides the brachial artery AIx without applying a transfer function. Similar to the Vicorder, there are no validation studies of the Arteriograph in pregnancy; however, it has been used widely in pregnancy research[7,25,26] and validated against aortic AIx obtained by cardiac catheterization in a non-pregnant cohort[13].

The advantages and disadvantages of commonly used devices for recording PWV and AIx are presented in Table 1.

ENDOTHELIAL FUNCTION

The endothelium lines the internal surface of arteries and is sensitive to changes in hemodynamic signals, responding by releasing a number of vasodilator substances, the most potent of which is nitric oxide (NO), or vasoconstrictors. Endothelial injury with resulting dysfunction is associated with atherosclerosis and cardiovascular events[27].

Endothelial function is commonly assessed by measurement of upper-arm flow-mediated dilatation (FMD) or forearm blood flow; although there is no consensus as to which technique provides more precise information, forearm blood flow measurement is generally considered the 'gold standard' for endothelial function testing (see Table 2 for a comparison of their advantages and disadvantages). Brachial artery FMD correlates with measures of coronary endothelial function[28,29]. Normal arteries dilate by 10–15% depending on the position of the cuff and equipment used[30]. By definition, if vasodilation does not reach 5%, there is overt endothelial dysfunction[29,30].

Flow-mediated dilatation (FMD) measurement

FMD measurement as described by Celermajer *et al.*[30] has been used extensively, with good reproducibility and low interobserver variability[31]. This technique requires an ultrasound system equipped with a high-frequency linear vascular probe, vascular software for two-dimensional and color Doppler imaging, and an internal ECG monitor so that each image frame of blood flow can be synchronized to the cardiac cycle. A stereotactic probe-holding device will limit measurement error due to micromovements of the probe by the operator.

Table 2 Techniques for measuring endothelial function

Technique	*Advantages*	*Disadvantages*
Flow-mediated dilatation	Non-intrusive Predicts outcome Relatively quick assessment	Considered a less precise method of assessment Expensive collateral equipment
Forearm blood flow	Currently gold standard Allows assessment of basal nitric oxide Strong correlation with cardiovascular outcome	Intrusive Requires specialist research setting Time-consuming

With the subject lying supine, a baseline longitudinal image of the brachial artery with clear visualization of the anterior and posterior intimal interfaces between the lumen and vessel wall is first acquired. Then, arterial occlusion is created using a forearm blood pressure cuff inflated to suprasystolic pressure for a standardized length of time. Subsequent cuff deflation induces a brief high-flow state through the brachial artery (reactive hyperemia) and the resulting increase in shear stress causes endothelium-dependent vasodilation. The longitudinal image of the artery is recorded continuously, from 30 s before to 2 min after cuff deflation. This continuous imaging period should be sufficient to capture peak arterial dilatation, which is reported to occur around 57 ± 15 s after cuff deflation in pregnant women[32,33]. At least 10 min of rest is needed after reactive hyperemia before another image is acquired to reflect the reestablished baseline conditions.

If the endothelium-independent vasodilation response is to be tested, an exogenous NO donor (usually nitroglycerin (glyceryl trinitrate, GTN) spray or sublingual tablet) is administered prior to the steps above, to determine the maximum obtainable vasodilator response 3–4 min after GTN administration. The observed endothelium-independent vasodilation reflects vascular smooth-muscle function.

FMD is calculated as the percentage change from the baseline diameter to the peak diameter in response to reactive hyperemia, using the following equation:

$$\text{FMD (\%)} = \big((\text{peak diameter} - \text{baseline diameter}) / \text{baseline diameter}\big) \times 100.$$

Forearm blood flow measurement

Resistance vessel function in the forearm is assessed by strain-gauge venous impedance plethysmography. This works on the principle that if venous return from the arm is obstructed and arterial inflow continues unimpeded, the forearm swells at a rate proportional to the rate of arterial inflow[34]. This procedure is generally carried out as follows: a wrist cuff is inflated to suprasystolic pressure and 60 s allowed to elapse before measurements commence. A second cuff is placed around the upper arm and inflated to around 40 mmHg (higher than venous pressure but lower than diastolic pressure) at intervals of 10 s with 5-s deflation, allowing venous emptying whilst not impeding arterial inflow. The arms are positioned above the heart using pads and cushions. A strain gauge is placed around the forearm and the changes in circumference (which reflect changes in forearm volume) are measured.

This test is most useful when comparing dose–response relationships of different drugs within a single study; however, drawbacks include reproducibility (due to variations in arterial pressure, initial forearm blood flow and forearm size) and the technique's more intrusive nature compared with FMD.

ARTERIAL FUNCTION STUDIES IN PREGNANCY

In normal pregnancy, there is a significant reduction in unadjusted aortic PWV from preconception to the second trimester (although the reduction is not significant for MAP-adjusted PWV). Unadjusted aortic PWV remains low or increases slightly in the third trimester and returns to baseline in the postpartum period[35,36]. Aortic AIx adjusted for heart rate (i.e. AIx-75) in normal pregnancy follows a pattern similar to that of aortic PWV, with the most significant changes occurring between prepregnancy and the early first trimester[37]. FMD increases in pregnancy until 32 weeks' gestation, then decreases significantly from 36 weeks[38,39].

Studies of arterial stiffness in complicated pregnancies have focused largely on pre-eclampsia, intrauterine growth restriction (IUGR), preterm birth and gestational diabetes (GDM)[7,26,40,41], disorders that are associated with a greater risk of a future cardiovascular event in the mother.

Arterial function in hypertensive disorders of pregnancy

All parameters of arterial stiffness have been found to differ significantly in pre-eclamptic women from those in normotensive pregnancies. In a systematic review of 23 studies evaluating the effect of pre-eclampsia on arterial stiffness, women with pre-eclampsia had increased arterial stiffness both during and after pregnancy, and to a greater extent than did women with gestational hypertension. More severe presentation of pre-eclampsia was associated with a greater degree of arterial stiffness[42]. It should be noted, however, that only a few of the studies included in the review adjusted arterial stiffness measurements for the important variables of maternal heart rate or blood pressure. Significantly higher levels of aortic PWV and AIx

have also been observed in the subclinical stage (as early as 11 weeks' gestation) of pre-eclampsia[23,41]; interestingly, the magnitude of aortic PWV increase in these early phases was similar to that seen in established pre-eclampsia. Cross-sectional and longitudinal studies that assessed arterial stiffness in the early subclinical stages have demonstrated the potential for indices of arterial stiffness as a screening test to predict subsequent development of early- and late-onset pre-eclampsia, especially when combined with other maternal variables, such as central systolic blood pressure[7,41].

Lower FMD has been found in the first and second trimesters in high-risk women who subsequently develop pre-eclampsia, compared with controls[43,44]. An increase in FMD has been observed 4–6 weeks postpartum in women who had pre-eclampsia, suggesting partial reversal of the endothelial dysfunction[45]. Very few studies of endothelial function in pregnancy have included both endothelial-dependent and endothelial-independent measurements; this may affect findings, as both processes are intricately related and vary considerably during pregnancy[19].

ARTERIAL FUNCTION IN FETAL GROWTH RESTRICTION

Very few studies have examined aortic PWV in isolated IUGR. In one study which reported on small-for-gestational-age (SGA) babies (i.e. a heterogeneous cohort of fetuses which were small, some of which were not growing well (IUGR) and others that were constitutionally small but healthy and growing normally), no differences were found in aortic PWV recorded in the first trimester[46]. In normal pregnancies, a relationship was found between aortic PWV in the third trimester and birth weight, with an increase of 1 m/s in aortic PWV associated with a decrease in birth-weight centile of 17.6%[47]. In pregnant women with chronic hypertension who subsequently developed both superimposed pre-eclampsia and IUGR, aortic AIx-75 was a determinant of birth weight, and was the only significantly elevated hemodynamic parameter in patients who developed IUGR but not superimposed pre-eclampsia[48]. Aortic AIx, while normal in women with normotensive SGA pregnancies, was elevated in women who later presented with pre-eclampsia and SGA fetuses. In postnatal women whose pregnancies were affected by IUGR, there was a persistent difference in FMD compared with controls[49]. This difference was not seen when comparing GTN responsiveness between the two groups, suggesting that the differences in FMD were due to endothelial rather than vascular smooth muscle dysfunction.

Arterial function in diabetes in pregnancy

Arterial stiffness indices are higher in women with established GDM and in those with pre-existing Type-2, but not Type-1, diabetes mellitus[50,51]. Furthermore, women who develop GDM have increased arterial stiffness which is evident from the first trimester of pregnancy, suggesting its potential predictive value[26]. Possible mechanisms to explain these associations include: (1) alterations in the composition of the extracellular matrix and arterial remodeling, due to hyperglycemia, and (2) oxidative stress, both of which lead to arterial stiffening. Additionally, diabetes is associated with reduced NO production, which may impair endothelial function.

RECOMMENDATIONS FOR ASSESSING ARTERIAL FUNCTION IN PREGNANCY

- Due to the rapid responses of sympathetic activity and the arterial system to internal and external influences, as many variables as possible should be standardized across all tests.
- Before any measurements are performed, time should be allowed for adequate acclimatization to the room in which the tests are to be carried out. In general, participants should rest in the position in which the tests are to be carried out (e.g. supine or sitting) for at least 5 min before the tests commence. For FMD measurements, a resting position of around 20 min is recommended[52].
- Room temperature should be set at approximately 22–24 °C to control for orthostatic changes. As several medications that are commonly taken in pregnancy can affect arterial function, it is generally recommended that participants refrain from taking such medication for at least four half-lives of the drug prior to testing, when possible and safe to do so. Drug and vitamin intake over the previous 24 h should be recorded and correlated to the results.
- It is recommended that participants abstain from caffeinated drinks for at least 4 h and smoking for 12 h prior to hemodynamic testing.
- In pregnancy, caval compression from the weight of the gravid uterus can affect maternal hemodynamics, so it is recommended that tests are carried out with the woman in the left lateral position. If longitudinal studies are to be performed, this position should also be standard even when the woman is not pregnant or in the first trimester.
- Comparison of results should also be adjusted for any neurohormonal perturbations associated with pregnancy and fertility; for example, phase of menstrual cycle when performing preconception studies or breastfeeding when performing postpartum assessments. Participants who have undergone hormonal stimulation, such as follicular priming in preparation for *in-vitro* fertilization, may have very different hemodynamics[53], and this should be taken into account when comparing them against women with spontaneous conception.

RECOMMENDATIONS FOR FUTURE RESEARCH

- Arterial function testing in pregnancy has focused largely on identifying different hemodynamic signatures

in pathological pregnancies. More large-scale studies are needed to assess and validate the role of arterial function parameters in predicting pregnancy complications, as well as assessing its prognostic value, whether alone or in combination with other biophysical and biochemical markers of metabolic dysfunction.
- Additionally, an understanding of arterial function changes between preconception and very early pregnancy in relation to pathological pregnancy is lacking, so longitudinal preconception work is needed.
- A few studies[54,55] in pregnancy have assessed the impact of therapy on arterial function, but larger-scale studies would be helpful in evaluating how and to what extent the maternal arterial system responds, and whether treatment options can be adjusted to optimize clinical outcome.
- To improve our understanding of changes in arterial stiffness independent of confounding factors, such as maternal heart rate or blood pressure, which can change significantly in disorders such as pre-eclampsia, studies should report appropriately adjusted parameters alongside raw data.

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