

# The Role of Central Aortic Blood Pressure Monitoring in the Management of Hypertensive Disorders of Pregnancy

## Executive Summary

- Hypertensive disorders of pregnancy occur in 1 in every 12 to 17 pregnancies. Approximately 25% of cases of gestational hypertension progress to preeclampsia. Proactive identification of populations at risk of preeclampsia is a necessary part of pregnancy management.
- Elevated central aortic pressure predicts preeclampsia. The risk of preeclampsia with elevated central aortic pressure appears to be more sensitive than with brachial pressure. Brachial and central aortic pressures provide complimentary information for risk prediction and management decisions.
- Measurements of central arterial pressures can be incorporated into the current approaches to hypertension management as the dual arterial pressure SphygmoCor XCEL device, the only FDA cleared medical device for non-invasive central arterial pressure waveform analysis for all adults, can provide both brachial and central aortic pressures in the same clinic setting.
- Incorporation of central aortic blood pressure monitoring into the treatment paradigm for hypertensive disorders of pregnancy can be utilized as follows: (a) confirmation of hypertension so that initiation of medication is more likely to be the correct decision for a patient, (b) avoiding initiation of medication when white coat hypertension is suspected, (c) confirmation that increased treatment may not be needed, and (d) targeting when to consider reduction of medication.
- Based on current technology, the availability of a non-invasive dual arterial pressure measurement system, the compelling clinical rationale and the clinical published research, incorporation of central aortic pressure monitoring, which is complementary to continued reliance on brachial pressure monitoring should be a part of the care of all pregnant women.

## Background

Hypertensive disorders of pregnancy are relatively common and occur in 1 in every 12 to 17 pregnancies among women ages 20 to 44.<sup>1</sup> Hypertension in pregnancy can be categorized as follows:

### 1. Chronic Hypertension

Hypertension prior to pregnancy or before 20 weeks of pregnancy. Women who have chronic hypertension may develop preeclampsia in the second or third trimester of pregnancy.<sup>2</sup>

## 2. Gestational Hypertension

Hypertension during pregnancy without proteinuria, other renal disorders, biochemical or hematologic disorders or cardiac dysfunction. It is typically diagnosed after 20 weeks of pregnancy or close to delivery. Gestational hypertension usually resolves after birth of the child. However, some women with gestational hypertension have a higher risk of developing chronic hypertension in the future. Approximately 25% of cases progress to preeclampsia.<sup>2,3</sup>

## 3. Preeclampsia/Eclampsia

The condition whereby a woman who previously had normal blood pressure develops hypertension and protein in the urine and/or other organ disorders after 20 weeks of pregnancy. Associated findings may include acute kidney injury, liver dysfunction, neurological features, hemolysis or thrombocytopenia and fetal growth restriction. Preeclampsia occurs in approximately 1 in 25 pregnancies in the United States.<sup>2,3</sup> Women with preeclampsia may develop eclampsia, which is defined by the new onset of seizures and/or coma. It is estimated that preeclampsia is responsible for >500,000 fetal and neonatal deaths and >70,000 maternal deaths globally.<sup>4</sup>

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## Diagnosis

Diagnosis is based on standard brachial artery blood pressure (BP) measurement, which is the standard of care during pregnancy. Office based BP is generally measured during each prenatal visit. Home BP monitoring including 24-hour ambulatory BP monitoring is a useful adjunct in diagnosis and is particularly useful to rule out white coat hypertension (WCH). Proteinuria is preferably assessed by screening with simple non-invasive testing (dipstick urinalysis). If positive, quantification is performed using a urine protein/creatinine ratio ( $\geq 30$  mg/mmol (0.3 mg/mg) is abnormal).

## Management

Management includes close follow-up and home-based BP monitoring. BP monitoring equipment ideally should have been validated in pregnant women by the manufacturer, although equipment is used without such validation. Pharmacotherapy is used to lower blood pressure to acceptable targets. BP target should be systolic of 110 to 140 mm Hg and diastolic of 85 mm Hg.<sup>5</sup> The choice of pharmacologic agents in pregnant women differs from standard hypertension management. Acceptable agents include oral methyldopa, labetalol, oxprenolol, and nifedipine.<sup>5</sup> The American College of Obstetricians and Gynecologists recommends that women with high risk factors for preeclampsia should be treated with low dose acetylsalicylic acid (ASA, aspirin) 81 mg between, ideally between 12 and 28 weeks (optimally before 16 weeks) and continued until delivery.<sup>6</sup> Low-dose aspirin prophylaxis should be considered for women with more than one of several moderate risk factors for preeclampsia. Risk factors include prior preeclampsia, chronic hypertension, pregestational diabetes, maternal BMI  $>30$  kg/m<sup>2</sup>, antiphospholipid syndrome and receipt of assisted reproduction.<sup>5,6</sup>

Preeclampsia requires intensive monitoring and specific care. Eclampsia is a medical emergency, therefore the goal of monitoring and treatment is to avoid this potentially fatal complication.

**Table 1:** Clinical risk assessment for preeclampsia\*7

Risk Level	Risk Factors	Recommendation
High**	<ul style="list-style-type: none"> <li>History of preeclampsia, especially when accompanied by an adverse outcome</li> <li>Multifetal gestation</li> <li>Chronic Hypertension</li> <li>Type 1 or 2 diabetes</li> <li>Renal disease</li> <li>Autoimmune disease (systemic lupus erythematosus or antiphospholipid syndrome)</li> </ul>	Recommend low-dose aspirin if the patient has one or more of these high-risk factors
Moderate***	<ul style="list-style-type: none"> <li>Nulliparity</li> <li>Obesity (BMI &gt; 30 kg/m<sup>2</sup>)</li> <li>Family history of preeclampsia (mother or sister)</li> <li>Sociodemographic characteristics (African American race, low socioeconomic status)</li> <li>Age 35 years or older</li> <li>Personal history factors (e.g., low birthweight or small for gestational age, previous adverse pregnancy outcome, more than 10-year pregnancy interval)</li> </ul>	Consider low-dose aspirin if the patient has more than one of these moderate-risk factors****
Low	<ul style="list-style-type: none"> <li>Previous uncomplicated full-term delivery</li> </ul>	Do not recommend low-dose aspirin

\*Includes only risk factors that can be obtained from the patient's medical history. Clinical measures, such as uterine artery Doppler ultrasonography, are not included.

\*\*Single risk factors that are consistently associated with the greatest risk of preeclampsia. The preeclampsia incidence rate would be approximately 8% or more in a pregnant woman with one or more of these risk factors.

\*\*\*A combination of multiple moderate-risk factors may be used by clinicians to identify women at high risk of preeclampsia. These risk factors are independently associated with moderate risk of preeclampsia, some more consistently than others.

\*\*\*\*Moderate-risk factors vary in their association with increased risk of preeclampsia.

\*Adapted from Committee on Practice Bulletins. The American College of Obstetricians and Gynecologists. Gestational hypertension and preeclampsia. *Obstetrics and Gynecology* 2020;135:e237-260.

The prophylactic use of low-dose aspirin starting in early pregnancy can potentially reduce the rate of preeclampsia by 50%. The National Institute for Health and Clinical Excellence (NICE) has recommended that (a) all pregnant women should be screened in the first trimester for the risk of preeclampsia, and (b) pregnant women at high risk for preeclampsia should be treated with aspirin.<sup>8</sup>

## Non-invasive Central Aortic Pressure Predicts Preeclampsia

Early recognition of gestational hypertension and those at risk for preeclampsia represents a clinically important management objective for women who are pregnant. Identification of those at-risk permits focusing of resources where the need is greatest in the population of pregnant woman and for the developing

fetus. Unlike the vast majority of patients with chronic hypertension, where end-organ damage develops over years to decades and acute events have been preceded by the gradual damage to the organ over time, pregnancy is a relatively short period where dramatic physiologic changes occur. The effects of preeclampsia and eclampsia can be acute and life-threatening to both the woman and the fetus. Therefore, tools that can identify those at risk and assist in management of gestational hypertension are necessary. Brachial blood pressure monitoring remains a key tool, but non-invasive central aortic pressure monitoring can provide additional data that augments current management approaches.<sup>9-11</sup> Of note, brachial and central blood pressures correlate but central pressure cannot reliably be predicted in an individual from their brachial pressure.<sup>11</sup> The following paragraphs describe data supporting the incorporation of central blood pressure monitoring into standard screening and for enhanced monitoring for those women at risk for preeclampsia.

In a prospective screening study, Khalil and colleagues (2009) investigated whether pulse wave analysis (PWA) performed during the first trimester can predict preeclampsia in 210 low-risk women.<sup>12</sup> Fourteen (6.7%) women developed pre-eclampsia. Eight of the 14 women developed pre-eclampsia before 34 weeks of gestation (early-onset pre-eclampsia). Augmentation Index (Alx) adjusted to a heart rate of 75 beats/minute (Alx-75) had a detection rate of 79% for all cases of pre-eclampsia and 88% for early-onset pre-eclampsia. The false positive rate was 11%. Mean brachial blood pressure was not predictive of preeclampsia in the population studied. A study of 32 women with gestational hypertension documented that central aortic systolic pressure and Alx appeared to be more predictive of the subsequent development of preeclampsia relative to brachial pressures.<sup>13</sup>

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In another publication from the same group, the predictive value of the combination of first-trimester serum placental protein 13 (PP13), uterine artery Doppler pulsatility index (PI) and Alx-75 was evaluated.<sup>14</sup> They also evaluated concurrent and contingent strategies using combinations of the above tests for assessing the risk of preeclampsia in high-risk women. A nested case-control study design was used. For each case of preeclampsia (n=42), five matched controls were randomly selected. Compared with controls, women who developed preeclampsia had lower PP13, higher uterine artery mean PI and higher Alx-75 ( $p<0.001$ ). The highest detection rate for preeclampsia (85.7% (95% CI, 71.5-94.6%)) and preeclampsia requiring delivery before 34 weeks (92.9% (95% CI, 66.1-99.8%)) was achieved by concurrent testing with all three markers. The false positive rate was 10%. The best contingency screening sequences for preeclampsia were (Alx-75 → PP13 → mean PI) and (PP13 → Alx-75 → mean PI), with an 86% detection rate with false-positive rates of 9 and 10%, respectively. In summary, the combination of first trimester PP13, uterine artery mean PI and pulse wave analysis can be useful for the prediction of preeclampsia in women at increased a-priori risk and may be useful in clinical practice.

A report in 2012 evaluated the potential value of assessment of central aortic systolic BP (cSBP), pulse wave velocity (PWV) and Alx at 11-13 weeks gestation in identifying women who subsequently develop pre-eclampsia.<sup>15</sup> Maternal history and characteristics were recorded and PWV, Alx-75 and cSBP measured. Women who developed pre-eclampsia (n=181) were compared to those in unaffected controls (n=6,766). In the pre-eclampsia group, compared to unaffected controls, there was an increase in Alx-75 ( $p<0.0001$ ), PWV ( $p<0.0001$ ) and cSBP ( $p<0.0001$ ). cSBP had the highest predictive value for preeclampsia. It was particularly

notable that in the group with chronic hypertension, in those who developed PE, compared to those who did not, the cSBP (1.29 vs.1.15 multiples of the median of the control group (MoM);  $p=0.001$ ) was increased but there was no significant difference in PWV (1.02 vs.1.00 MoM;  $p=0.921$ ) or Alx-75 (1.37 vs. 1.21 MoM;  $p=0.104$ ). The authors concluded that compared with women who remain normotensive, women who develop pre-eclampsia have higher cSBP and arterial stiffness (as measured by PWV and Alx-75), which is apparent from the first trimester of pregnancy.

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A report by Anvi et al sought to examine whether PWA could discriminate between normal and hypertensive pregnancies.<sup>16</sup> One hundred pregnant women were studied: five with severe pre-eclampsia, 27 with gestational hypertension, 14 with chronic hypertension and 54 with normal pregnancy. Augmentation pressure, Alx and Alx-75 were significantly higher in women with gestational hypertension and pre-eclampsia compared with normal pregnancies and women with chronic hypertension ( $p < 0.05$  for all). There were no significant differences between normal pregnancies and women with chronic hypertension ( $p > 0.05$  for all comparisons). Alx and augmentation pressure were significantly different among groups even after adjusting for peripheral BP. The study provides further support to the utility of adding measurement of central aortic pressures to standard brachial blood pressure measurements.

Marozio et al examined the possible correlation between pulse wave analysis (PWA) parameters measured during the first trimester of pregnancy in normotensive, low-risk women, and the development of hypertensive disorders later in pregnancy.<sup>17</sup> The study population ( $n=1,648$ ) was recruited at the time of prenatal screening for chromosomal abnormalities (11+0 to 12+6 weeks of gestation). The values of central aortic systolic pressure, central aortic diastolic pressure, central aortic mean pressure, central aortic pulse pressure, and Alx-75 measured in the first trimester of pregnancy were significantly higher in the women who later developed hypertensive disorders of pregnancy than in those who remained normotensive ( $p<0.0001$  for all except for aortic pulse pressure ( $p=0.014$ )). The aortic systolic pressure (sensitivity 72.6%; specificity 59.6%) was found to be the best predictor for the later development of hypertension.

**Table 2:** Predictive values of PWA parameters recorded at 11 – 13 weeks gestation in relation to later development of hypertensive disorders of pregnancy\*

Variable	Sensitivity (95% CI)	Specificity (95% CI)	AUC (95% CI)
aortic systolic pressure	72.6 (62.5, 81.3)	59.6 (55.7, 62.1)	0.70 (0.68, 0.72)
aortic diastolic pressure	55.2 (44.7, 65.4)	77.6 (75.5, 79.7)	0.68 (0.66, 0.70)
aortic mean pressure	65.6 (55.2, 75.0)	67.3 (64.9, 69.7)	0.70 (0.68, 0.72)
aortic pulse pressure	63.5 (53.1, 73.1)	51.0 (48.5, 53.5)	0.58 (0.55, 0.60)
Alx-75	56.3 (45.8, 66.6)	64.5 (62.0, 66.9)	0.62 (0.60, 0.64)
Mean Ut-PI	42.2 (34.2, 50.6)	65.9 (63.9, 67.9)	0.54 (0.52, 0.56)

AUC = area under the curve, Ut-PI = uterine artery pulsatility index

Brachial BP was not predictive of the subsequent development of hypertensive disorders of pregnancy, which is consistent with the view that, while correlated, brachial BP and central aortic BP are not interchangeable. The incidence of preterm hypertensive disorders of pregnancy, particularly of preterm, early-onset preeclampsia, was too low to allow subgroup analysis of the predictive performance of PWA parameters. The authors concluded that in normotensive, low-risk pregnant women, PWA may be useful for the early detection of risk for the development of hypertensive disorders of pregnancy and may allow for targeted surveillance and preventive intervention.

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A prospective longitudinal study of hemodynamics in 245 women at risk of pre-eclampsia documented that elevation in systolic aortic pressure that are associated with the development of pre-term pre-eclampsia may occur in women who are normotensive early in pregnancy.

Hausvater and colleagues conducted a systematic review and meta-analysis to investigate the association between preeclampsia and arterial stiffness as measured by PWA and pulse wave velocity (PWV).<sup>18</sup> Twenty-three relevant studies were included. A significant increase in all arterial stiffness indices combined was observed in women with preeclampsia compared to women with normotensive pregnancies [standardized mean difference 1.62, 95% confidence interval (CI) 0.73-2.50]. Carotid-femoral pulse wave velocity and augmentation index (AIx) were significantly increased, whereas carotid-radial PWV increase did not reach significance. Significant increases in arterial stiffness measurements were noted in women with preeclampsia compared with those with gestational hypertension. The data indicate that arterial stiffness measurements may be useful in predicting preeclampsia and may play a role in the increased risk of future cardiovascular complications seen in women with a history of preeclampsia.

A separate systematic review and meta-analysis of published literature examined whether PWA and PWV measurements during pregnancy differed between healthy patients and patients with placental-mediated diseases including preeclampsia, small for gestational age, fetal death, and placental abruption.<sup>19</sup> A total of 2,806 citations and 36 studies were reviewed. Nine studies (n=15,923) were selected for further quantitative assessment. Compared with healthy pregnancy, measures from PWA and PWV that reflected arterial stiffness were consistently increased among pregnant women who subsequently developed preeclampsia during all trimesters. In the first trimester, mean AIx-75 (%) in the preeclampsia group was significantly higher with estimated standardized mean difference (SMD) of 0.90 [95% confidence intervals (95% CI) 0.07-1.73; p=0.034]. In the second trimester, the preeclampsia group had significantly higher PWV (m/s) with estimated SMD of 1.26 (95% CI 0.22-2.30; p=0.018). Concerning the small for gestational age group, mean (SD) AIx (%) was greater during the second trimester only (65.5 (15.6) vs. 57.0 (11.2), p<0.01).

**Table 3:** Estimated standardized mean difference and corresponding 95% confidence intervals (lower, upper) between the preeclampsia and healthy groups for arterial stiffness measurements (pulse wave velocity, augmentation index, augmentation index 75) at three trimesters.

Parameter	First Trimester	Second Trimester	Third Trimester
PWV (m/s)	0.85 (-1.07, 2.78)	1.26 (0.22, 2.30) <sup>1</sup>	0.49 (0.20, 0.78) <sup>2</sup>
Alx (%)	0.38 (-0.18, 0.93)	0.19 (-0.06, 0.44)	0.48 (0.20, 0.77) <sup>3</sup>
Alx-75 (%)	0.90 (0.07, 1.73) <sup>4</sup>	0.05 (-0.46, 0.56)	No study

<sup>1</sup>p=0.018, <sup>2</sup>p<0.001, <sup>3</sup>p=0.001, <sup>4</sup>p=0.034

\*Adapted from Osman et al. Association between arterial stiffness and wave reflection with subsequent development of placental-mediated diseases during pregnancy: Findings of a systematic review and meta-analysis. J Hypertension 2018;36:1005-14.

The analyses indicate that there is significant increase in arterial stiffness as assessed by PWA and PWV among pregnant women who subsequently developed preeclampsia and small for gestational age fetuses and are consistent with considering a role for central aortic pressure evaluation during pregnancy.

### Incorporating Central Aortic Pressure Assessment into Prenatal Care

The data from multiple publications indicate that central aortic pulse wave analysis (PWA) can be used to identify pregnant women at risk for preeclampsia. Expert consensus statements have documented and recommended that risk factor identification for gestational hypertension and preeclampsia be part of prenatal care.<sup>7</sup> PWA should be included in standard care as increases in Alx-75 and central aortic systolic pressure (cSBP) are risk factors that clearly can be identified in the first trimester. cSBP appears to provide complimentary and additional data to that of brachial systolic BP (i.e., the tests are not redundant). The identification of elevated PWA variables as risk factors for preeclampsia should therefore warrant consideration of enhanced monitoring (e.g., enhanced monitoring – office and home-based) and preventive therapeutic decisions (e.g., prescription of low-dose aspirin).

Hypertension management through the addition of non-invasive measurements of central aortic pressures has the potential to improve care through: (a) refining requirements for BP monitoring, (b) decreasing over-treatment, (c) early identification for earlier or more aggressive treatment, and (d) decreasing the overall cost of care (e.g., use of tools such as ambulatory blood pressure monitoring (ABPM), drug costs).

Identifying the requirements and amount of medication is critical to controlling gestational hypertension.

The following table provides examples where central aortic blood pressure monitoring may positively impact the treatment of gestational hypertension:

**Table 4:** Examples of clinical utility of measuring both brachial and central aortic blood pressure.

CLINICAL USE	BRACHIAL BP	CENTRAL BP
Confirming hypertension (drug prescription is optimized)	Elevated	Elevated
Suspicion of white coat hypertension	Elevated	Normal or Low
Avoidance of increased drug prescription	Borderline high	Normal or Low
Consideration of reducing drug prescription (patients receiving at least one anti-hypertensive medication)	Normal (particularly when there is suspected medication adverse effects)	Low (or extended period of normal)



The publications and data described in the previous sections indicate that the adjunctive measurement of central pressures provides clinically important patient care information. The provision of both peripheral and central pressures can occur during the same office visit, is available within a dual arterial pressure monitoring device (SphygmoCor XCEL), is clinically appropriate, and a cost-effective approach to identifying risk for preeclampsia and managing gestational hypertension.

## Summary and Conclusions

The following is a summary of the key discussion points:

Hypertensive disorders of pregnancy occur in 1 in every 12 to 17 pregnancies. Approximately 25% of cases of gestational hypertension progress to preeclampsia. Proactive identification of populations at risk of preeclampsia is a necessary part of pregnancy management.

Elevated central aortic pressure predicts preeclampsia. The risk of preeclampsia with elevated central aortic pressure appears to be more sensitive than with brachial pressure. Brachial and central aortic pressures provide complimentary information for risk prediction and management decisions.

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