SphygmoCor and Pregnancy/Preeclampsia

Summary

During pregnancy, women undergo major physical changes, not least of which is those that occur within the cardiovascular system. Hypertension is a common medical problem encountered during pregnancy and hypertensive disorders increase the risk of serious complications for both mother and child.

Hypertensive disorders in pregnancy can be classified as:

(a) chronic hypertension (hypertension predates the pregnancy or has on onset before 20 weeks gestation) and

(b) hypertension that develops after 20 weeks gestation which can result in

   (i) gestational hypertension (hypertension alone)

   (ii) preeclampsia (hypertension with proteinuria and multi-organ dysfunction) which can rapidly deteriorate to eclampsia (occurrence of seizures in a patient with preeclampsia).

While brachial blood pressure is routinely monitored throughout pregnancy, it is not a sensitive enough measure to distinguish preeclampsia from other types of hypertension or to predict pre-eclampsia in those at risk [1].

The ability to distinguish between hypertensive disorders and identify those women who have an increased risk of preeclampsia can lead to better management of hypertensive disorders during pregnancy and therefore better outcomes for both for both mother and child.

Background

Hypertensive disorders of pregnancy, in particular preeclampsia are a leading cause of maternal and neonatal morbidity and mortality [2].

Chronic hypertension is defined as a blood pressure of greater than 140mmHg/90mmHg before pregnancy or before 20 weeks gestation. In contrast, gestational hypertension refers to high blood pressure occurring after 20 weeks of gestation and normalising postpartum. Preeclampsia is diagnosed when hypertension and proteinuria are both present often with edema and usually occurs after the 32nd week and is considered as early onset preeclampsia if it occurs before this time. Preeclampsia may also arise as late as 4-6 weeks postpartum. Occasionally, preeclampsia may progress to the more serious condition of eclampsia, characterized by seizures and carries a risk of maternal morbidity.

In the United States and the United Kingdom approximately 5% of pregnancies are complicated by preeclampsia and of these patients, 1-2% progress to eclampsia [3, 4]. It is estimated that these rates are higher in developing countries. An estimated 50,000 women die annually from preeclampsia worldwide [5].

The presence of hypertension during pregnancy is also associated with a two-fold increase in the risk of gestational diabetes mellitus [6]. In addition, a history of preeclampsia increases a women’s subsequent risk of vascular disease, including hypertension, ischaemic heart disease, myocardial infarction and stroke [7].
The increased risk of complications is not limited to the mother; babies of women with hypertensive disorders during pregnancy are more likely to suffer adverse outcomes than those of women without hypertension [4].

A large cross-sectional study observing more than 250,000 women and their infants showed that women with gestational hypertension were at a 30% greater risk of death or major morbidity and women with pre-eclampsia had a 400% increased risk, compared to women without hypertension [1].

Although preeclampsia is not preventable, early diagnosis, careful monitoring and aggressive treatment is crucial in preventing mortality [4, 8].

**Pulse Wave Analysis**

Arterial stiffness is an independent predictor of cardiovascular events and mortality even in healthy individuals. Pulse wave analysis has become a valuable clinical tool outside of pregnancy, particularly in the assessment of patients with hypertension, renal disease and diabetes.

There is a large body of evidence showing that increased arterial stiffness is a basic cause of hypertension [9]. Increased arterial stiffness is observed as an increase in aortic pulse wave velocity (PWV) and an increased aortic augmentation index (AIx) caused, in turn, by the early return of the reflected pressure wave in the stiffer peripheral arteries.

During the last decade, the role of pulse wave analysis to measure central blood pressure and arterial stiffness in the assessment, management and prediction of preeclampsia has been investigated with promising results.

**Normal Pregnancy**

In normal pregnancy aortic stiffness has been shown to vary throughout the pregnancy, reaching its lowest point in second trimester and rising again in the third trimester. This has been shown in cross-sectional studies [10, 11] and recently in longitudinal studies [10, 12], as illustrated in Figure 1. When individual women were followed throughout pregnancy a significant fall in AIx was observed in the second trimester [10] followed by a significant rise in the third trimester [10, 12]. When observing healthy pregnant women in two different ethnic groups (Caucasian and Afrocaribbean), no significant difference was observed [10].

![Figure 1. Augmentation Index (AIx) measured in women during normal pregnancy. The individual raw values are plotted with regression lines of mean, 5% and 95% centiles. The vertical lines indicate mean, 2 and 95% centiles of healthy non-pregnant women. (From: Macedo ML, Luminoso D, Savvidou MD, et al. Maternal wave reflections and arterial stiffness in normal pregnancy as assessed by applanation tonometry. Hypertension 2008,51:1047-1051.)](image)
Aortic AIx has been shown to be significantly lower in pregnant women, in each of the three trimesters of pregnancy, compared to non-pregnant women [13, 10, 11], yet no difference was observed in aortic (or radial) PWV [11]. Two large cross-sectional studies have also shown a significant decrease in central systolic and diastolic blood pressure compared with healthy non-pregnant women [10, 11].

However, in normotensive pregnancies, maternal aortic PWV has been found to be significantly associated with lower birth weight independent of mean blood pressure [14]. An increase of 1 m/s in aortic PWV was associated with a decrease in birth weight centiles of 17%. Fetal growth is a principal issue in antenatal observations and birth weight centiles are regarded as important measures of pregnancy outcome. Potentially, higher aortic stiffness, even in normotensive pregnancies, may reflect inadequate plasma volume expansion, that in turn impedes optimal fetal growth [14].

**Gestational hypertension and preeclampsia**

Central blood pressures and aortic stiffness have been shown to be increased in the third trimester in women with hypertensive disorders, particularly in preeclampsia.

A number of studies [15, 16, 17, 18] have investigated the change in pulse wave analysis indices in the third trimester across the spectrum of hypertensive disorders. Central pressures (systolic, diastolic and pulse pressures), along with AIx and augmentation pressure were found to be significantly higher in gestational hypertension (and chronic hypertension) and preeclampsia compared to normal pregnancy. Furthermore, aortic AIx (and augmentation pressure) showed clear separation in preeclampsia compared to gestational hypertension and normal pregnancy [16], as shown in figure 1.

![Figure 2](image-url) Augustation index measured during pregnancy in women with normal pregnancy, gestational hypertension and preeclampsia. (From Spasojevic M, Smith SA, Morris JM and Gallery ED. Peripheral arterial pulse wave analysis in women with pre-eclampsia and gestational hypertension. BJOG 2005,112:1475-1478.)

Similarly, aortic stiffness (aortic PWV) has been shown to be significantly higher in the presence of gestational hypertension [15] and pre-eclampsia [15, 12].

A follow-up measurement at 6 weeks postpartum was observed in two studies with contrasting results [16, 19]. The earlier study showed that both AIx and aortic PWV after 6 weeks postpartum, the aortic AIx values in women with gestational hypertension and pre-eclampsia had returned to normal non-pregnant levels [16], while a later study found that these values remained elevated compared with normal pregnancy [19].
These studies suggest that measures of arterial stiffness, such as aortic AIx and aortic PWV may provide a clear distinction between those women with uncomplicated gestational hypertension and those who progress to pre-eclampsia compared to normal pregnancy.

A technique to predict preeclampsia

The ability to accurately identify women at risk of preeclampsia would have real clinical benefits. A recent study [20] performed pulse wave analysis on 210 pregnant women in the first trimester to determine if the pulse wave analysis AP and AIx indices could predict preeclampsia. Fourteen women developed preeclampsia, three of these developed severe preeclampsia and these were compared against the remaining 196 women as the control group. For a false positive rate of 11% PWA predicted 79% of women who went on to develop preeclampsia and 88% of those who went on to develop severe early onset preeclampsia. Early onset preeclampsia is the most severe end of the hypertensive disorder spectrum.

The authors acknowledge that the study had too few numbers for a firm conclusion to be drawn; but these results suggest that first trimester pulse wave analysis assessment could play a significant role as a predictive test for subsequent development of preeclampsia and this measurement warrants further investigation in larger patient groups.

Assessment of antihypertensive treatment

Pulse wave analysis has been extensively used outside of pregnancy to assess various medications including antihypertensives and importantly a number of these studies have shown that despite similar effects on peripheral blood pressure, differential results can be seen on central pressures. Central pressure has been shown to be a powerful predictor of cardiovascular events and in the Strong Heart Study of 3,500 high risk adults, central pulse pressure was 50% better than brachial blood pressure in predicting cardiovascular events [21]. The variability between central pressure and brachial pressure has been studied in 11,000 individuals and shown that central pressure cannot be derived from brachial pressure but must be measured [22].

Not all antihypertensive medications are safe for use during pregnancy and use of antihypertensive drugs differs among centres. Drug selection is aimed at reducing maternal risk and is largely based on safety to the fetus. Methyldopa is considered first line treatment for pregnant women with chronic hypertension and other antihypertensives may be acceptable, with the exception of ACE inhibitors and ARBs [23].

The effect of a standard antihypertensive treatment in pregnancy was investigated in a group of 80 women presenting with hypertensive disorders, 51 with preeclampsia and 29 with gestational hypertension [18]. A control group of 80 pregnant women not requiring medication that might affect blood pressure was included. Women with preeclampsia and gestational hypertension both exhibited significantly higher central systolic pressure, AP and AIx compared to the control group. Furthermore, AP and AIx were also significantly higher in early onset preeclampsia compared to late onset and severe preeclampsia compared to mild preeclampsia. Antihypertensive therapy with alpha methyldopa resulted in significant improvement in AP and AIx in women with preeclampsia, but not in women with gestational hypertension.

While this study assessed the effect of the antihypertensive before and only once after treatment (48 hours), the results show the possibility of pulse wave analysis having an important role in the assessment of treatment in hypertensive disorders in pregnancy.

Perspective

A number of studies have now shown that pulse wave analysis has the ability to distinguish between women with gestational hypertension and those with preeclampsia. Some studies have
also been able to different and predict women who may develop the severe form of early onset preeclampsia. These studies offer an insight into the vascular effects of pregnancy and the early detection of pregnancies complicated with hypertensive disorders and establishes the basis for further investigation into the role of pulse wave analysis in the assessment and possible prediction of preeclampsia. Furthermore early work showing the effect of treatment in preeclampsia provides a promising foray into assessment of medication and treatment in hypertensive disorders in pregnancy.

Non-invasive assessment of central blood pressure and arterial stiffness can be performed with the SphygmoCor system. This is a simple, reproducible and well validated device that uses applanation tonometry to derive the central aortic pressure waveform using a pressure waveform recorded at the radial artery. Analysis of the waveform provides key parameters including central arterial pressure and indices and arterial stiffness such as augmentation pressure and augmentation index. The SphygmoCor system also allows for non-invasive PWV measurements to be performed measuring the stiffness in the carotid-femoral (elastic) and carotid-radial (muscular) part of the arterial tree.

References


