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Henna Kärkkäinen

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ABSTRACT

During pregnancy, extensive changes in cardiovascular physiology are needed to adapt the woman's body to the needs of the feto-maternal unit. In complicated pregnancies, such as preeclamptic, hypertensive or diabetic pregnancies the cardiovascular adaptation can be impaired. A history of preeclampsia, gestational hypertension or gestational diabetes mellitus (GDM) is associated with the risk of cardiovascular diseases and events in subsequent decades, although the incidence of significant cardiovascular complications in women of child-bearing age is low. Arterial stiffness is an early marker for the development of cardiovascular diseases and there are numerous related studies measuring it during pregnancy. However, the optimal method of assessing the future risk in pregnant women is not known. The objective of this study was to assess arterial stiffness in normal and complicated pregnancies. The method used was ambulatory arterial stiffness index (AASI), which is based on an individual's 24-hour ambulatory blood pressure measurement (ABPM) values. The study population consisted of 123 women who were recruited from the Kuopio University Hospital maternity clinic or the antenatal department for the Complicated Pregnancy Study during the years 2002-2007. The women were examined during the third trimester of pregnancy and at three months postpartum. Thirty-two women had an uncomplicated singleton pregnancy, 11 had a twin pregnancy, 10 had a pregnancy complicated with gestational hypertension and 18 with preeclampsia. 52 women had GDM, 10 of whom had to use insulin to control their glucose values. AASI did not change in normal uncomplicated singleton or twin pregnancies. The women with GDM were the only group in which significant changes occurred. After delivery, the GDM women using insulin during pregnancy displayed a significantly higher AASI as an indication of stiffer arteries when they were compared to healthy pregnant controls. In the GDM women on diet, AASI decreased significantly after delivery, although the mothers probably lapsed from their strict diet. However, three months postpartum, women in both GDM groups exhibited marked cardiovascular risk factors; their lipid and glucose levels and BMI values were significantly higher than in the controls. Nevertheless, since the changes in the pregnancy complications were small and not linear, it is concluded that AASI was not sufficiently sensitive to reveal the changes in arterial stiffness during pregnancy.

The Data from the Cardiovascular Risk in Young Finns Study was used to evaluate the carotid artery elasticity during pregnancy. The study population consisted of 94 pregnant women and 99 matched controls, divided into three groups according to the gestational weeks. It was found that carotid artery stiffness increased towards the end of pregnancy and this was not dependent on the maternal hyperlipidemia or the pregnancy-related increase in the diameter of the carotid artery. This phenomenon may actually be an appropriate adaptation to the hemodynamic changes such as an increase in cardiac output and expansion of the plasma volume in pregnancy.

In conclusion, the importance of arterial stiffness as a risk factor for cardiovascular events has resulted in much research attempting to devise a method to assess this parameter and subsequently to identify patients with greater than normal cardiovascular risks. Pregnancy opens up a window through which to view the future cardiovascular risks, and at this stage, interventions would be very beneficial. In this study no harmful stiffening was detected in the arteries of the pregnant women. The only unfavorable changes in AASI were detected in postpartum values of GDM women requiring insulin during pregnancy, who, in particular, should be informed about their risks.

National Library of Medical Classification: WQ 248, WQ 215, WG 595.C2, WG 106
Medical Subject Headings: Pregnancy; Blood Pressure Monitoring, Ambulatory; Vascular Stiffness; Diabetes, Gestational; Pre-Eclampsia; Carotid Arteries

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TIIVISTELMÄ

Raskauden aikana naisen verenkiertoelimistö joutuu sopeutumaan suuriin muutoksiin, jotta istukan toiminta ja sitä kautta kasvavan sikiön hyvinvointi saadaan turvattua. Raskauden aikana ilmenevissä verenpainetaudissa ja diabeteksessa sekä pre-eklampsiassa eli raskausmyrkytyksessä tässä sopeutumisessa on häiriöitä ja näihin raskauskomplikaatioihin liittyykin suurentunut sairastuvuus sydän- ja verisuonitauteihin myöhemmällä iällä. Valtimoiden lisääntynyt jäykkyys on varhainen merkki suurentuneesta sydän- ja verisuonitautiriskistä. Tutkimuksia valtimojäykkyydestä on tehty myös raskauden aikana, mutta selvyyttä parhaasta menetelmästä sen mittaamiseen ei ole.

Tässä tutkimuksessa haluttiin mitata valtimojäykkyyttä normaaleissa ja komplisoituneissa raskauksissa. Käyttämämme menetelmä oli AASI (ambulatory arterial stiffness index) -indeksi, joka perustuu koko vuorokauden kestoiseen jatkuvaan verenpainemittaukseen. Raskauskomplikaatiotutkimukseen (RASKOMP) osallistui vuosina 2002- 2007 123 naista, jotka olivat joko Kuopion Yliopistollisen Sairaalan äitiyspoliklinikan tai synnytysosaston potilaita ja olivat antaneet suostumuksensa tutkimukseen. 32 naisella oli normaali yksisikiöinen raskaus. 11 naista odotti kaksosia, 10:llä oli raskaudenaikainen verenpainetauti ja 18:lla oli pre-eklampsia. Raskausdiabetes oli 52 naisella, joista 10 tarvitsi insuliinihoitoa. Naiset tutkittiin raskauden viimeisellä kolmanneksella ja kolme kuukautta synnytyksen jälkeen. AASI ei muuttunut normaaleissa yksisikiöissä tai kaksosraskauksissa. Insuliinihoitoista raskausdiabetesta sairastaneilla nähtiin synnytyksen jälkeen korkeampi AASI- arvo merkkinä jäykemmistä valtimoista kuin normaaliryhmässä. Ruokavaliohoitoista raskausdiabetesta sairastaneilla AASI laski synnytyksen jälkeen, vaikka naiset luultavasti luopuivat tiukasta ruokavaliostaan. Molemmissa raskausdiabetesryhmissä nähtiin synnytyksen jälkeisissä tutkimuksissa normaaliraskausryhmää korkeammat veren rasva- ja sokeriarvot ja korkeampi painoindeksi, jotka kaikki ovat tunnettuja sydän- ja verisuonisairauksien riskitekijöitä. Koko tutkimuksessa AASI- arvojen muutokset olivat pieniä, joten johtopäätöksenä voimme sanoa, että AASI ei todennäköisesti ole tarpeeksi herkkä menetelmä mittaamaan muutoksia valtimojäykkyydessä raskaana olevilla naisilla.

LASERI- tutkimuksen aineistosta tutkimme raskaudenaikaisia muutoksia kaulavaltimon jäykkyydessä. Tutkimusaineistoon sisältyi 94 raskaana olevaa naista, jotka jaettiin kolmeen ryhmään raskausviikkojen mukaan. Heille oli valittu 99 ei-raskaana olevaa verrokkia. Löydöksemme oli raskauden edetessä tapahtuva kaulavaltimon jäykistyminen, joka ei liittynyt odottavan äidin veren rasva-arvojen nousuun eikä raskauteen kuuluvaan kaulavaltimon läpimitan kasvuun. Kaulasuonten jäykistyminen voi olla välttämätön fysiologinen vaste raskauden aiheuttamiin verenkiertoelimistön muutoksiin, kuten sydämen iskutilavuuden ja plasman tilavuuden kasvuun.

Valtimojäykkyyden tärkeä merkitys sydän- ja verisuonitautien riskitekijänä on innostanut tutkijoita etsimään menetelmiä sen mittaamiseksi, jotta ne yksilöt, joilla on suurentunut riski, voitaisiin tunnistaa. Raskaus haastaa äidin verenkiertoelimistön ja antaa mahdollisuuden nähdä hänen taipumuksensa sydän- ja verisuonisairauksiin. Tässä vaiheessa elämäntapoihin puuttuminen olisi hyvin hyödyllistä myöhemmän sairastumisen estämiseksi. Tutkimuksessamme havaitsimme haitallisia muutoksia valtimojäykkyydessä AASI-indeksillä mitattuna ainoastaan insuliinihoitoisilla raskausdiabeetikoilla 3 kuukautta synnytyksen jälkeen. Heitä tulisi erityisesti informoida kasautuvasta sydän- ja verisuonitautiriskistä ja kannustaa tarvittaviin elämäntapamuutoksiin.

Luokitus: WQ 248, WQ 215, WG 595.C2, WG 106
Yleinen suomalainen asiasanasto: raskaus, valtimot, jäykkyys, raskausdiabetes, pre-eklampsia, verenpaine, kaulavaltimot

To Aarne, Reeta, Ellinoora and Antti

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Kuopio, October 2013

Henna Kärkkäinen

List of the original publications

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I Kärkkäinen H, Heiskanen N, Saarelainen H, Valtonen P, Lyyra-Laitinen T, Laitinen T, Vanninen E, Heinonen S. Ambulatory arterial stiffness index is unchanged in uncomplicated third-trimester singleton and twin pregnancies. *Acta Obstetricia et Gynecologica Scandinavica 90:516-523, 2011.*

II Kärkkäinen H, Laitinen T, Heiskanen N, Saarelainen H, Valtonen P, Lyyra-Laitinen T, Vanninen E, Heinonen S. Need for insulin to control gestational diabetes is reflected in the ambulatory arterial stiffness index. *BMC Pregnancy & Childbirth. 13:9, 2013.*

III Kärkkäinen H, Saarelainen H, Laitinen T, Heiskanen N, Valtonen P, Laitinen T, Vanninen E, Heinonen S. Ambulatory arterial stiffness index and nocturnal blood pressure dipping in pregnancies complicated by hypertension. *Clinical Physiology and Functional Imaging. 2013 Jun 19. doi:10.1111/cpf.12063. [Epub ahead of print]*

IV Kärkkäinen H, Saarelainen H, Valtonen P, Laitinen T, Raitakari OT, Juonala M, Kähönen M, Hutri-Kähönen N, Heinonen S, Laitinen T. Carotid artery elasticity decreases during pregnancy – The Cardiovascular Risk in Young Finns Study. *Submitted.*

Contents

Abbreviations

AASI	ambulatory arterial stiffness index
ABPM	ambulatory blood pressure measurement
AIx	augmentation index
ASDPRI	ambulatory systolic-diastolic pressure regression index
BBD	diameter of brachial artery
BMI	body mass index
BP	blood pressure
CAC	carotid artery compliance
CAD	carotid artery distensibility
CCD	diameter of the common carotid artery
CI	confidence interval
CRP	C-reactive protein
DBP	diastolic blood pressure
DM	diabetes mellitus
ECG	electrocardiography
Einc	incremental modulus of elasticity
FMD	flow mediated dilation
GDM	gestational diabetes mellitus
HDL	high-density lipoprotein
HOMA-IR	homeostasis model assessment of insulin resistance
HR	hazard ratio
IL-6	interleukin -6
IMT	intima-media thickness
LDL	low-density lipoprotein
NO	nitric oxide
OGTT	oral glucose tolerance test
OR	odds ratio
PWV	pulse wave velocity
RR	relative risk, risk ratio
SBP	systolic blood pressure
SD	standard deviation
SI	stiffness index
SMD	standardized mean difference
YEM	Young's elastic modulus

1 Introduction

Arterial stiffness is a phenomenon that has been studied for over a century. In 1914 MacWilliam et al. wrote in The British Medical Journal: "The left ventricle pumping blood into the normally elastic arterial system of tubes produces lower systolic and higher diastolic pressures than would be present in a system of relatively inelastic or stiffened vessels."(Macwilliam 1914). Early models of pulsatile hemodynamics were based on the Windkessel concept. The Windkessel model for describing blood flow in the heart was originally developed and published by Stephen Hales in 1733 and Otto Frank in 1899 (Sagawa et al. 1990). In fire trucks, intermittent pumping by the firemen was converted into a constant water stream by adding an air chamber or "Windkessel" above the water tank to buffer the pulsations. The human arteries, especially the aorta, have the same buffering effect to produce a steady blood flow instead of pulsatile spurts. However, the human arterial tree is much more complicated than a firemen's hose, with branch points and changing calipers and muscularity in peripheral arteries and reflecting waves which amplify the original wave. For this reason in recent decades, the research in arterial stiffness has focused on the pulse wave velocity and wave reflections. Arterial stiffness is known to be an important risk factor for cardiovascular events and therefore its assessment is increasingly used in clinical examinations.

The ambulatory arterial stiffness index (AASI) was originally described in 2006, and it has been shown to be correlated not only with other arterial stiffness assessment techniques, but more importantly, also with cardiovascular events and death. AASI is easily accessed from 24-h ambulatory blood measurement results, with no other measuring device being needed. During pregnancy, extensive changes are needed in cardiovascular physiology in order to adapt a woman's body to the needs of the feto-maternal unit. These include an increase in cardiac output, expansion of the plasma volume, reductions in vascular resistance and systemic blood pressure, the appearance of insulin resistance and hyperlipidemia. Arterial compliance is increased as an adaptation to all these changes to balance the reduced resistance and to ensure that there is perfusion to all organs. However, in complicated pregnancies, such as preeclamptic, hypertensive or diabetic pregnancies, the cardiovascular adaptation can be impaired.

Gestational diabetes mellitus and gestational hypertension are very common problems due to the increased prevalence of obesity and advanced maternal age. Preeclampsia is a prevalent, potentially dangerous, pregnancy complication, which still accounts for an estimated 70000 maternal deaths per year worldwide (Abalos et al. 2013). The aim of the Complicated Pregnancy Study was to explore the pathophysiology behind these conditions to help predict the diseases and treat the women suffering from them more effectively. It was hoped that AASI could be a method for screening and identifying potential pregnant women who will subsequently develop preeclampsia. Another aim was to clarify the metabolic situation at three months after these complicated pregnancies and if there would be any consequences for maternal health.

2 Review of the literature

2.1 BASIC PRINCIPLES OF ARTERIAL STIFFNESS

Human arteries are more than tubes through which the blood is pumped from the heart to peripheral organs; they are elastic and have a dampening function to provide a steady flow within peripheral tissues. The most elastic artery is the aorta, which does most of the smoothing and distends significantly during systole. During diastole, the recovery of the aorta pushes blood forward through the arterial tree and augments the filling of coronary arteries. (Berne et al. 1996, Tomlinson 2012). When moving from the aorta to peripheral arteries, there is a progressive loss of the elasticity and increasing muscularity in the walls of arteries. This means that peripheral arteries are stiffer than central arteries in healthy subjects. In general, the elastic properties of conduit arteries vary; caused by different molecular, cellular and histological structures along the arterial tree (Laurent et al. 2006).

The heart generates a forward arterial pressure wave that returns as reflected waves from the periphery. The branch points along the arterial tree and the high level of resistance in periphery generate retrograde waves, which amplify the pressure wave. In elastic arteries, the reflected waves coincide with the diastole, consequently raising diastolic pressure, whereas in stiffer arteries, the reflected pulse waves move faster and coincide with the systole, elevating systolic pressure, thus increasing the gap between systolic and diastolic blood pressure, i.e. pulse pressure (Ross et al. 1991, O'Rourke et al. 2002a). Arterial stiffness is associated with a widened pulse pressure.

2.1.1 The factors changing arterial stiffness

Arterial stiffness increases with advancing age. Arterial calcification and its progression to atherosclerotic plaques are not the only reasons; elastin fragmentation and degradation leads to loading of collagen fibers. The artery wall thickens and the arteries dilate. Furthermore, endothelial function is affected via diminished NO (nitric oxide**)** synthesis (Kinlay et al. 2001, McEniery et al. 2006) or contraction of vascular smooth muscle cells (Gaballa et al. 1998). Subclinical inflammation as reflected by CRP is also an important predictor of aortic stiffness (McEniery et al. 2010) and an individual can also have a genetic predisposition.

Hypertension (Benetos et al. 2002), diabetes mellitus (Cameron et al. 2007) and impaired fasting glucose (Paik et al. 2012), obesity (Zebekakis et al. 2005), smoking (Mahmud et al. 2003), hypercholesterolemia (Pitsavos et al. 1998), kidney disease (Wang et al. 2005) and components of the metabolic syndrome such as waist circumference (Sipilä et al. 2007) are conditions known to be linked to increased arterial stiffness. Stiffening of the arteries can, to some extent, be modified by drugs, or by exercise training improving endothelial function in the carotid artery (Tanaka et al. 2013) and in the aorta (Heydari et al. 2013) or by reducing salt intake (He et al. 2009). An attenuating effect of garlic on age- and

pressure-related increases in aortic stiffness has also been described (Breithaupt-Grogler et al. 1997).

2.1.2 The importance of arterial stiffness

The arterial stiffness is highly relevant to cardiovascular diseases for several reasons 1. It is centrally involved in the pathogenesis of systolic hypertension, 2. it affects the ability of the arteries to comply with the blood ejected from the heart, 3. it modifies the pulsatility needed to supply enough blood into target organs such as brain and 4. it is influenced by many factors which are known to promote cardiovascular diseases (Chirinos 2012). There are many studies, emphasizing that arterial stiffness can be considered as an intermediate endpoint for cardiovascular events (Laurent et al. 2001), and therefore its assessment is increasingly becoming a routine in clinical examination, particularly in hypertensive patients as a way of predicting future cardiovascular events (Wang et al. 2008).

2.2 ASSESSMENT OF ARTERIAL STIFFNESS

The most accurate assessments of arterial stiffness are achieved invasively by catheterization, but noninvasive methods are much more convenient and cheaper. In this review, only the noninvasive methods will be discussed.

The methodologies used to assess arterial stiffness can be categorized into three groups: 1) analysis of the pulse transit time, 2) waveform analysis of the arterial pulse and 3) direct measurement of arterial geometry and pressure**.** It is also possible to classify the stiffness type measured as, being 1) local, when a small section of an artery is under study; 2) regional when a segment of the arterial tree is evaluated or 3) systemic, when the whole circulation is assessed (Laurent et al. 2006).

Since the assessment of arterial stiffness can be done in several ways, the terms in different studies can be confusing. Compliance and distensibility are computable quantities, but are often used mixed with the word “stiffness”. Thus arterial stiffness represents a useful term to depict alterations in the mechanical properties of the arterial tree (Hamilton et al. 2007). Noninvasive methods of assessment of arteries are gathered in Table 1.

Table 1. Methods of noninvasive assessment of arterial stiffness, endothelial function, and atherosclerosis

Method	Application	Advantage	Limitation
Pulse wave velocity	Arterial stiffness	Most reliable measurement, "golden standard",prognostic value, clinical experience	Location- and blood pressure-dependent, no data on arterial structure
Change in vessel diameter to pressure(for example carotid stiffness)	Arterial stiffness	Direct measurement of arterial stiffness, reliable	Heavily dependent on blood pressure measurement
Augmentation indexes	Arterial stiffness	Easy to use, clinical experience,	Affected by many variables such as heart rate and vasomotor tone, relatively poor at predicting outcome
Ambulatory artery stiffness index	Arterial stiffness	Simple measurement, low cost	To be validated to predict clinical outcome
Flow-mediated dilation	Endothelial dysfunction	Reliable and correlated with invasive measurement of endothelial function, clinical experience needed	Technically demanding, requires a standardized protocol
Carotid intima-media thickness	Atherosclerosis	Reliable and direct measurement of atherosclerotic plaque by ultrasound, clinical experience, easy to use	Unable to describe lipids and plaque composition, technically demanding

2.2.1 Pulse wave velocity

Pulse wave velocity (PWV) is a derivative of pulse transit time and it can be categorized as a regional measurement; usually the descending aorta is the region being measured. The arterial pulse wave is recorded transcutaneously in a proximal artery, often the common carotid; and at a more distal, often femoral, artery. PWV is calculated as $D/\Delta T$, D for the distance between these two points and ΔT for the pulse arrival time delay between the points. Figure 1 shows the assessment of carotid-femoral PWV. It was demonstrated to be an independent predictor of cardiovascular risk for the first time in the study of Blacher et al. They studied 241 patients with end-stage renal disease and determined that the OR for PWV >12 versus <9.4 m/s was 5.4 (95% CI, 2.4 to 11.9) for all-cause mortality and 5.9 (95% CI, 2.3 to 15.5) for cardiovascular mortality. For each PWV increase of 1 m/s in their study population, all-cause mortality–adjusted OR was 1.39 (95% CI, 1.19 to 1.62) (Blacher et al. 1999). Nowadays it is clear that the PWV value increases with arterial stiffening and there are large clinical studies demonstrating that aortic stiffness measured by PWV is an independent predictor for cardiovascular morbidity and total mortality (Laurent et al. 2006). Vlachopoulos et al. performed a meta-analysis of 17 longitudinal studies that evaluated aortic PWV and followed up 15,877 subjects for a mean of 7.7 years. They claimed that the pooled relative risk (RR) of clinical events in high versus low aortic PWV subjects was increased for total cardiovascular events 2.26 (95%CI: 1.89 to 2.70), cardiovascular mortality 2.02 (95%CI: 1.68 to 2.42), and all-cause mortality 1.90 (95%CI: 1.61 to 2.24) (Vlachopoulos et al. 2010b).

PWV is considered as the "most hallowed" or "golden standard" measurement of arterial stiffness (O'Rourke et al. 2002b, Laurent et al. 2006). In 2010, the PWV results of 11 092 healthy individuals were combined to establish the first reference and normal values for PWV after standardizing the results for different methods of PWV measurement (Reference Values for Arterial Stiffness' Collaboration 2010).

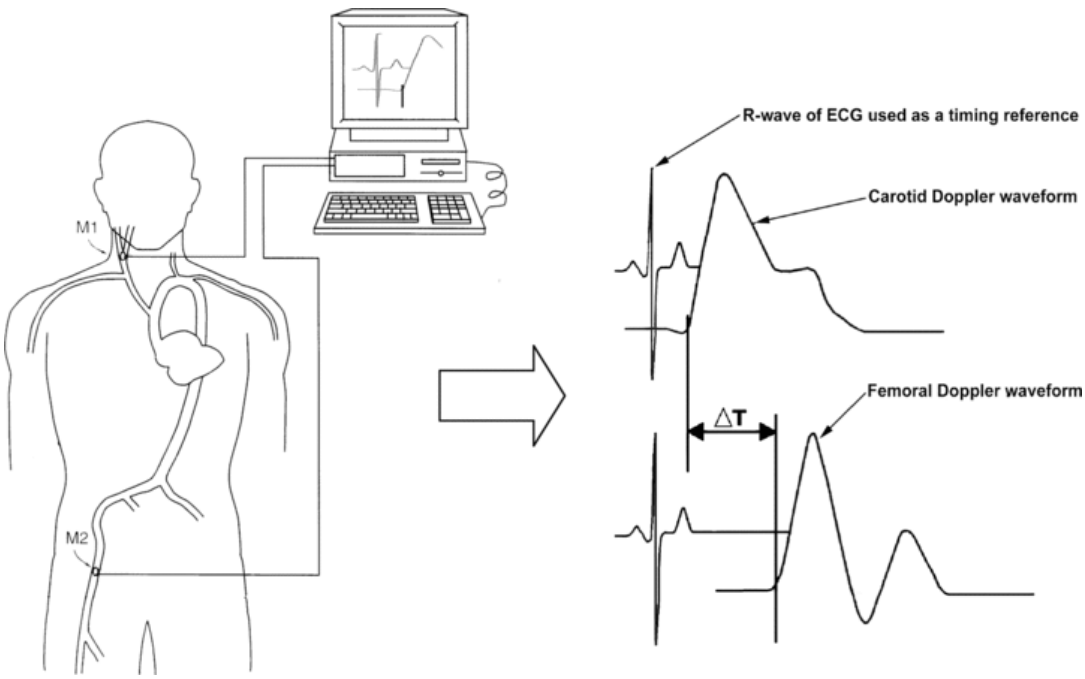


Figure 1. Illustration of arterial PWV. The arterial pulse wave is recorded at a proximal artery (the common carotid, labeled as M1 on the left penal) and at a more distal artery (the femoral, labeled as M2). PWV is calculated as D (meters)/ΔT (seconds), where D is the distance between the two recording sites and ΔT is the time delay between the arrival of the pulse wave at these two points and compared using the R-wave of the ECG shown here. A number of devices can automatically calculate the PWV between any two-user selected/defined locations (With permission of Wang et al. 2008).

2.2.2 Pulse wave analysis

The augmentation index (AIx) calculated from the arterial pulse waveform is widely used to evaluate arterial stiffness (Kelly et al. 1989). AIx is the percentage of central pulse pressure attributable to the systolic pressure rise enhanced by the reflected pulse wave. It is determined from pulse waves of carotid or radial artery using applanation tonometry. Figure 2 shows examples of aortic pulse waveforms. AIx is dependent on the changes in heart rate and other alterations in cardiac and vascular function, for example drug effects (Wilkinson et al. 2001), and its use as an index for arterial stiffness has been criticized, as it may not be an accurate tool with which to assess central aortic stiffness (Mitchell 2004, Hughes et al. 2013). However, it has been shown to be associated with cardiovascular risk (Nurnberger et al. 2002). In a meta-analysis of 11 longitudinal studies and 5648 subjects with a mean follow-up of 45 months, it was found that the age- and risk-factor-adjusted pooled relative risk (RR) for total cardiovascular events was 1.318 (95% CI 1.093–1.588)

and for all-cause mortality 1.384 (95% CI 1.192–1.606) for a 10% absolute increase of central augmentation index (Vlachopoulos et al. 2010a).

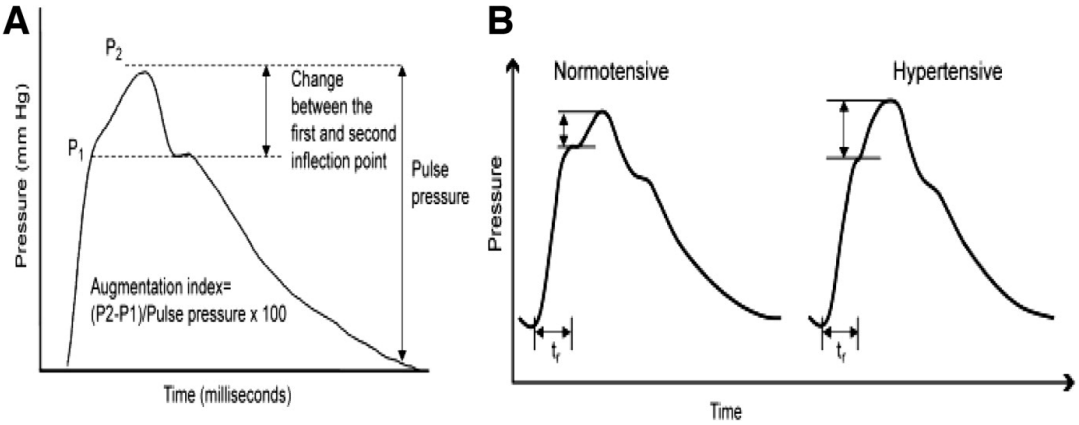


Figure 2. Examples of aortic pulse waveforms. A, Typical ascending aortic pulse waveform, showing 2 systolic peaks (P1 and P2). The augmentation index is calculated as the difference between P2 and P1, expressed as percentage of the pulse pressure. The designation P1 is the first inflection point; P2 is the second inflection point. B, In hypertensive disorders, arterial wall stiffness is increased; the arterial pulse wave travels faster, so the resulting wave reaches the advancing wave in systole, resulting in greater augmentation of the systolic peak. Time, tr is the time to reach the reflected wave. (With permission from Rogers et al. 2010.)

2.2.3 Ambulatory arterial stiffness index

Despite its acknowledged pathophysiological and clinical value aortic PWV has not become a routine procedure in daily clinical use for examining the level of cardiovascular risk of hypertensive patients. This is mainly due to the need of dedicated and expensive equipment for its assessment and being demanding to use. These difficulties have stimulated research and encouraged development of new technologies to estimate arterial stiffness in a more convenient manner, based on the obvious consideration that an easier and less expensive technique would allow a much larger diffusion of this assessment in daily practice (Parati et al. 2012). The ambulatory arterial stiffness index (AASI) is an index, which is defined as 1 minus the regression slope of the plot of diastolic on systolic blood pressure values in individual subjects and can be determined noninvasively from 24-hour ambulatory blood pressure recordings. Thus, AASI reflects the dynamic changes between systolic and diastolic blood pressure, which are attributable to the hemodynamic arterio-ventricular properties, including arterial stiffness (Kollias et al. 2012). The stiffer the arterial tree, the closer the AASI is to value one. AASI was published for the first time

in 2006 (Li et al. 2006b, Dolan et al. 2006a). Dolan et al. hypothesized that the dynamic relationship between diastolic and systolic blood pressure over 24h would provide a method to measure the stiffness of the arterial wall. This hypothesis was based on a concept published almost a century previously, in 1914 by MacWilliam et al. (Macwilliam, 1914). Dolan et al. based their hypothesis on the following hemodynamic principles: 1) in an elastic artery, the changes in systolic and diastolic blood pressure occur in parallel throughout the blood pressure range. In stiffer arteries, due to the enhanced pulse wave reflection, there will be a greater change in systolic pressure, in fact, diastolic pressure may even decrease; i.e. pulse pressure rises. 2) The relationship between arterial stiffness and distending pressure is not linear; since the mean arterial pressure increases, stiffness increases exponentially (Mitchell 2004) and 3) mean arterial pressure shows considerable diurnal variability, increasing with activity and declining with rest and sleep (Dolan et al. 2006b). Hence, the relationship between diastolic and systolic blood pressure in an individual might provide an insight into arterial function.

The relationship between diastolic and systolic pressure has been classically examined with the pulse pressure which is primarily affected by the stroke volume, the aortic compliance and the diastolic flow from the aorta i.e. the ejection function of the left ventricle (Ross et al. 1991). Thus, since AASI is considered to relate to pulse pressure, then a change in any of these variables would be expected to evoke a change in AASI.

The value of AASI can be very different in individuals with similar 24-hour blood pressure recordings and similar pulse pressures as shown in Figure 3 from Dolan et al.
The normal values of AASI are proposed to be <0.50 at age 20 and <0.70 at age 80 (Li et al. 2006b). The term ambulatory systolic-diastolic pressure regression index (ASDPRI) has been used occasionally to describe AASI (Aznaouridis et al. 2012, Sobiczewski et al. 2013).

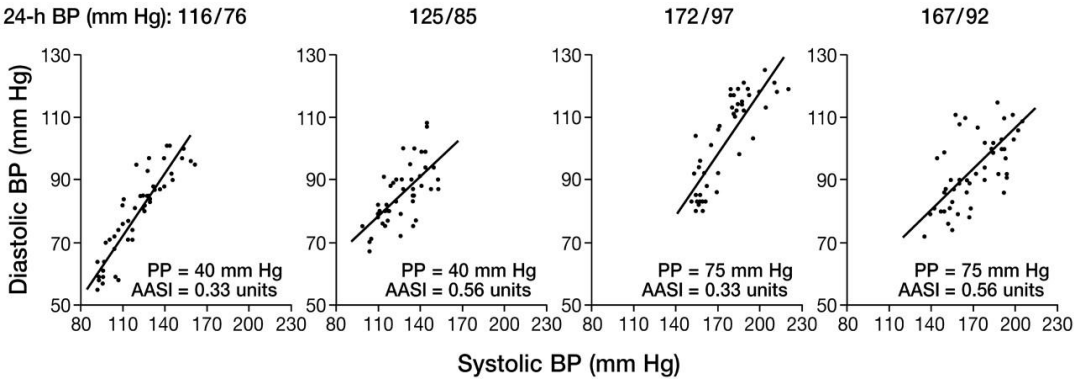


Figure 3. Plots of diastolic blood pressure regressed on systolic blood pressure in 4 different subjects. BP, PP, and AASI indicate blood pressure, the 24-hour pulse pressure, and the AASI, respectively. For similar levels of 24-hour BP and PP, the AASI varied from 0.33 to 0.56. (With permission from Dolan et al.2006a.)

2.2.3.1 Strengths and limitations of ambulatory arterial stiffness index

Many of the devices needed to assess arterial stiffness are expensive and not readily accessible. The only procedure needed to measure AASI is the 24-hour ambulatory blood pressure measurement (ABPM), and this might well explain the growing interest in assessing this additional piece of information which can be derived from ambulatory blood pressure values. AASI is easily assessed and the measurement is not technically demanding and it does not require great expertise to interpret the result. It is non-invasive and relatively cheap. Nonetheless, AASI has been criticized for its poor reproducibility (Gosse et al. 2007) and for the lack of a straightforward correlation between it and other measurements of arterial stiffness (Schillaci et al. 2007, Jerrard-Dunne et al. 2008). Based on six studies, the reproducibility of AASI in two assessments appeared to be modest with repeatability coefficient ranging from 0.24 to 0.40 (Kollias et al. 2012).

The relationship between AASI and other stiffness methods has been studied. The correlation with pulse pressure is clear. AASI has been shown to correlate with pulse wave velocity and the augmentation index (Li et al. 2006b, Bastos et al. 2010, Gomez-Marcos et al. 2012), but in one study an adjustment for age negated the correlation (Jerrard-Dunne et al. 2008). The possible pathophysiology behind AASI has been discussed extensively. Schillaci et al. evaluated AASI in 515 untreated patients and found out that: (1) it was strongly dependent on the degree of nocturnal blood pressure fall in hypertensive patients and (2) the relation between AASI and a widely accepted measure of aortic stiffness, such as pulse wave velocity, was weak and importantly affected by other factors (Schillaci et al. 2007). In addition, large variations in an individual subject's blood pressure values could affect AASI, and a goodness-of-fit of the AASI regression line might be useful and impact on the correlations between AASI and established determinants (Adiyaman et al. 2008).

A comprehensive review of AASI studies has noted that in most of the studies AASI is positively associated with age, systolic blood pressure and 24 h pulse pressure and inversely correlates with nocturnal decline in systolic and diastolic blood pressure values (Kollias et al. 2012). In addition, body mass index, heart rate, glucose and lipid values have been shown to be associated with AASI by some investigators. Nevertheless, even though AASI might not be an unequivocal evaluator of arterial stiffness, it still can represent a useful marker of cardiovascular risk (Parati et al. 2012).

Table 2. The prognostic value of AASI, prospective studies

Study	**Study population**	**N**	**Age**	**Follow-up time (years)**	**AASI**	**Main findings (adjusted hazard ratio)**
Dolan et al. 2006	Untreated, 76% hypertensives	11291	54.6 ± 14.6	5.3	0.41 ± 0.16	Mortality per 1 SD increase: CV 1.08; stroke 1.21*; cardiac 1.03
Kikuya et al. 2007	Population study, 49% hypertensives	1542	61.7 ± 10.7	13.3	0.46 ± 0.10	Highest quartile of AASI: mortality 1.16, CV 1.29, stroke 1.40.
Hansen et al. 2006	Random sample	1829	55.5 ± 10.7	9.4	0.56 ± 0.14	Per 1 SD increase CV events 1.06, stroke 1.62*
Ben-Dov et al. 2008	Population study, 59% hypertensives	2918	56 ± 16	7.0	0.48	All-cause mortality per 1 SD increase 1.14
Muxfeldt et al. 2010	Resistant hypertension	547	65.9 ± 11.3	4.8	0.55 ± 0.14	Per 1 SD increase composite endpoint 1.46*, all-cause mortality 1.03, CV mortality 1.39
Gosse et al. 2008	Hypertensives	469	54 ± 14	5.8	0.54 ± 0.14	RR for CV events in highest vs. lowest AASI tertile 2.8*
Palmas et al. 2009	Diabetics	1178	71	2.5	0.52	Highest tertile all-cause mortality 1.36*
Bastos et al. 2010	Hypertensives, 47% untreated	1200	50.7 ± 12.7	8.2	0.30 ± 0.18	Per 1SD increase: CV events 1.67, stroke 1.10
Sobiczewski et al. 2013	Coronary artery stenosis	615	63.7 ± 9.4	6.7	0.32 ± 0.1	OR for acute coronary syndrome 3.6*, for major adverse cardiovascular event 2.5* and for all-cause death 2.7*
Laugesen et al. 2012	Diabetes type II	108	57	9.5	0.40	AASI ≥ median value → higher risk of CV events (P<0.05)*

SD= standard deviation, CV= cardiovascular, RR= risk ratio, OR= odds ratio. Adjusted hazard ratio = adjusted with sex, age, mean arterial pressure, body mass index, smoking, diabetes mellitus, and history of cardiovascular disease. * = a significant result.

2.2.3.2 Clinical implications of ambulatory arterial stiffness index

ABPM is nowadays recommended in the diagnosis of hypertension, as described in British guideline (Krause et al. 2011). In Finnish Current Care, its use is recommended in certain problematic situations such as in drug-resistant or white coat hypertension (Working group set up by the Finnish Medical Society Duodecim and the Finnish Hypertension Society 2009). One can predict that ABPM will be used more frequently and when one has its results, then the AASI can be estimated rather easily. Kollias et al. speculated in their review of AASI that it would be valuable to develop a composite index of cardiovascular risk from ABPM and AASI (Kollias et al. 2012).

However, even currently, AASI provides a marker for future outcome. It can be used to detect arterial dysfunction at a younger age than can be obtained from pulse pressure (Li et al. 2006b). AASI predicts cardiovascular death (Li et al. 2006c) and stroke (Bastos et al. 2010, Hansen et al. 2006) more precisely than classical risk factors (Dolan et al. 2006a, Kikuya et al. 2007) and is associated with target organ damage in individuals with arterial hypertension, i.e. left ventricular hypertrophy, carotid artery abnormalities and reduced renal function (Leoncini et al. 2006, Mule et al. 2008). It has also been shown to predict the progression of albuminuria in type II diabetes (Palmas et al. 2007). In addition, poor adherence to antihypertensive therapy has been postulated to be associated with increased standard AASI (Berni et al. 2011). A modified AASI has been found to be independently associated with all-cause mortality (Ben-Dov et al. 2008). The studies of the prognostic value of AASI are listed in Table 2.

2.2.4 Local stiffness indexes based on pressure and dimension

The local arterial stiffness of superficial arteries can be assessed with ultrasound devices (Laurent et al. 2006). The diameter of the artery is determined during diastole and then during systole and in most cases the change can be related to the distending pressure measured at the brachial artery. This method requires no assumptions, but instead is a direct determination. Elastic properties such as distensibility and compliance coefficients, stiffness index and Young's elastic modulus can be obtained from these ultrasound measurements. Furthermore, the intima media thickness (IMT), which is a useful parameter for assessing the condition of the vasculature, may well be determined in the same session (Laurent et al. 2006).

2.2.4.1 Carotid artery stiffness

The common carotid artery is a readily accessible artery and thus it is easy to study with ultrasound. In addition, the frequent presence of atherosclerosis in this artery makes it particularly suitable and clinically relevant. However, ultrasound measurement requires expertise and takes a longer time than measuring PWV. When one examines common carotid artery, then IMT will be a useful marker of early atherosclerosis and it is predictive of future cardiovascular diseases (Lorenz et al. 2007). Several carotid artery elasticity indexes such as Young's elastic modulus (YEM), stiffness index (SI) and carotid distensibility (CAD) or carotid compliance (CAC) can be evaluated ultrasonically. Young's elastic modulus provides an estimate of arterial stiffness which is independent of artery wall thickness. Distensibility and compliance measures the ability of the artery to expand in response to pressure; distensibility reflects the relative change in diameter with compliance

representing the absolute. Stiffness index is considered to be relatively independent of blood pressure.

2.2.4.2 Clinical implications of carotid artery stiffness measurements

Increased carotid stiffness is a characteristic feature of cardiovascular aging, hypertension and, to a lesser extent, atherosclerosis (Safar 1996). Common carotid artery stiffness has been shown to correlate in young adults with age, BMI, waist circumference, systolic and diastolic blood pressures, heart rate, pulse pressure, triglyceride levels, total cholesterol to HDL cholesterol ratio, insulin and glucose levels (Urbina et al. 2004). In the Cardiovascular Risk in Young Finns Study, it was found that cardiovascular risk factors identified in childhood and adolescence predicted reduced carotid artery elasticity in adulthood (Juonala et al. 2005). In addition, women are known to have significantly greater carotid artery compliance than men (Marlatt et al. 2012). Common carotid artery IMT and distensibility are markers of cardiovascular risk in patients with risk factors (Simons et al. 1999, Giannarelli et al. 2012). Common carotid artery stiffness has also been shown to be combined with diastolic dysfunction of the left ventricle (Myung et al. 2012). Blacher et al. described a significant association between carotid artery stiffness and cardiovascular as well as total mortality in end-stage renal patients (Blacher et al. 2001). Haluska et al. studied 719 primary prevention patients and found that the carotid distensibility coefficient was inversely correlated with mortality (HR=0.54; p=0.02) (Haluska et al. 2010). Another example of its utility is the fact that cessation of smoking significantly enhanced carotid artery elasticity in otherwise healthy men (Zhang et al. 2012).

2.3 NOCTURNAL BLOOD PRESSURE DIPPING

Blood pressure (BP) displays a circadian pattern i.e. there is a blood pressure reduction (dipping) during the night-time. The normal ranges for ABPM are as follows: average daytime ABPM of less than 135/85 mmHg and average night-time ABPM less than 120/70 mmHg, but even lower values are recommended, particularly in high-risk groups such as diabetic patients (O'Brien et al. 2005). Nocturnal blood pressure dipping means the difference between daytime and night-time blood pressures. Intra-arterial studies have revealed that BP falls from day- to night-time or from awake to sleep (Littler 1979, Mancia et al. 1983). The dippers/nondippers classification was introduced by O'Brien et al., who described an association between non-dipping and stroke (O'Brien et al. 1988). The hypothesis was that target organ damage and prognosis would be worse when the BP load is persistent for the whole 24-hours compared to the situation when it was limited to the daytime hours (Verdecchia 2000). Attempts have been made to evaluate the level of the normal dipping pattern (Staessen et al. 1997), but the threshold values have ranged from 10% or 10/5 mmHg to 0% (i.e. no reduction in BP from day to night or a higher BP during the night than during the day) (Verdecchia 2000). Currently, a 10%-20% fall has been established as a cutoff for a normal BP daytime-night-time reduction (Baumann et al. 2008; Chobanian et al. 2003) and those individuals with less than 10% nocturnal fall are called nondippers, with >10% but <20% nocturnal fall are called dippers, and with >20% extreme dippers. The diurnal variations in the blood pressure values of a dipper and a nondipper are shown in Figure 4. The rate of dipping can only be studied by ABPM. The cuff is placed around the arm for 24 hours' time and the blood pressure measurement system is

programmed to record pressure at certain intervals, for example 15-minute intervals during the daytime and 30-minute intervals during the night-time. In 1985, Parati et al. published a study where they examined the possibility that cuff inflations would disturb the sleep and the natural nocturnal fall in BP (Parati et al. 1985). They monitored 48 h BP in 10 hospitalized subjects intra-arterially and also at the same time they measured BP 24 h non-invasively, with the cuff inflation intervals at 30 minutes during the night-time. It was shown that the noninvasive brachial BP monitoring did not differ from the intra-arterially measured 24-hour blood pressures, and this was important support for the use of these devices during sleep.

The definition of daytime and night-time can vary; it can be diary-based or it can be a fixed time interval.

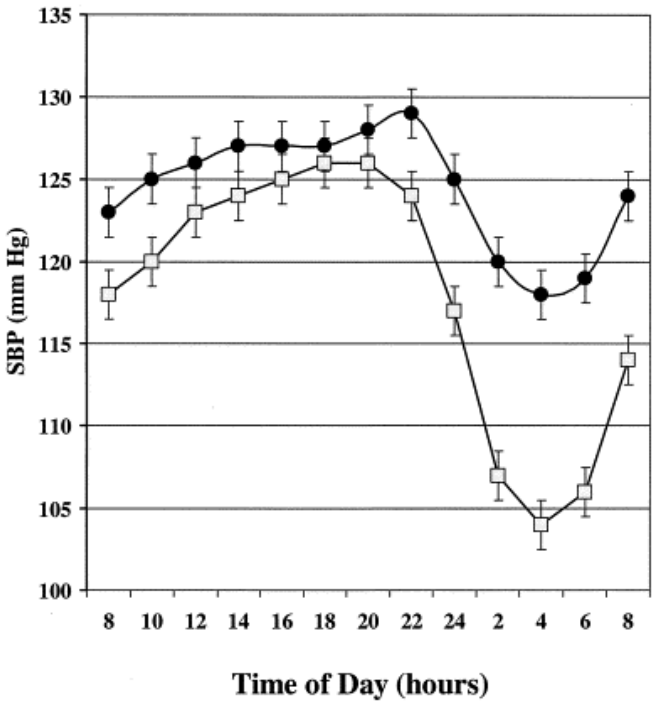


Figure 4. Diurnal variation in systolic blood pressure (SBP) in dippers (boxes connected by lines) (n=116) and nondippers (filled circles connected by lines) (n=56). (With permission from Sherwood et al. 2002.)

2.3.1 Clinical implications of nocturnal blood pressure dipping patterns

The exact mechanisms of nondipping are not fully understood. It has been proposed that nondippers have a reduced circadian fluctuation in their autonomic functions in comparison to dippers (Kohara et al. 1995) and the activity of the sympathetic nervous system may contribute to the individual variation (Sherwood et al. 2002). The nondipping phenomenon is more frequently found in individuals with kidney diseases, neuropathies, diabetes, sleep apnea, autonomic dysfunction as well as malignant or secondary hypertension (Kanbay et al. 2008). The lack of the nocturnal fall in blood pressure is known to be a risk factor for many target organ failures such as left ventricle hypertrophy, and

intima media thickening (Cuspidi et al. 2001), congestive heart failure (Ingelsson et al. 2006), microalbuminuria (Tsioufis et al. 2002), progression of renal damage, cardiovascular events (Verdecchia et al. 1993) and total mortality (Ohkubo et al. 1997, Fagard et al. 2008). In two Japanese studies, non-dipping as well as extreme dipping (>20%) have been shown to be associated with advanced silent cerebrovascular damage (Kario et al. 1996, Watanabe et al. 1996). There are reports that the blunted reduction in nocturnal BP correlated with increased pulse pressure and increased arterial stiffness (Lekakis et al. 2005).

In conclusion, there is a growing evidence to indicate that nondipping is associated with a greater risk of target organ damage and a worse prognosis (Routledge et al. 2007).
AASI is strongly dependent on the degree of nocturnal blood pressure fall. AASI displays a much stronger relationship with BP variability than with BP itself, evidence that AASI is not only a parameter for arterial stiffness but also for reflecting BP variability (Lee et al., 2011).

2.4 ARTERIAL STIFFNESS AND DIPPING DURING PREGNANCY

Maternal hemodynamic and metabolic adaptations to pregnancy include an increase in cardiac output, expansion of the plasma volume, reductions in vascular resistance and systemic blood pressure, insulin resistance and hyperlipidemia (Poppas et al. 1997, Edouard et al. 1998, Saarelainen et al. 2006, Ulusoy et al. 2006). The increase in arterial compliance during pregnancy is relevant from several physiological perspectives. First, this appears to be one of the body's adaptive mechanisms to accommodate the larger intravascular volume without increasing mean arterial pressure. Second, increased arterial compliance balances the effects of reduced vascular resistance and helps to maintain the efficiency of energy transfer from the left ventricle to the arteries. Third, increased compliance also helps to preserve perfusion pressure to the coronary arteries and other vital organs (Poppas et al. 1997). The cardiovascular changes occurring during pregnancy are shown in Figure 5.

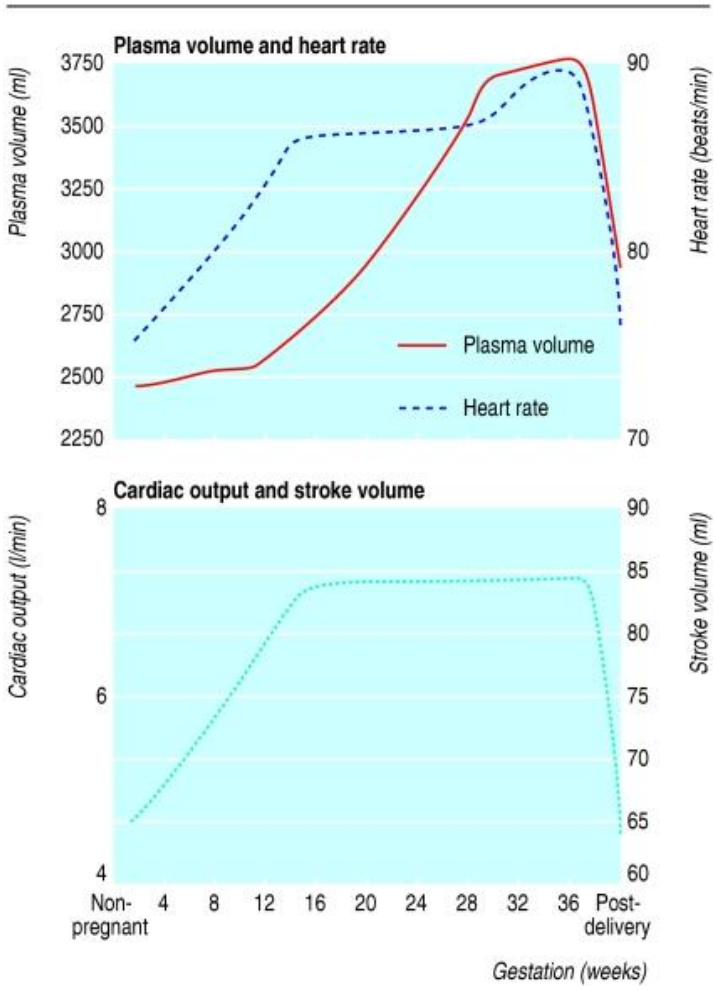


Figure 5. The cardiovascular changes in normal pregnancy (With permission from Uebing et al., 2006, modified from original figure of Thorne, 2004.)

While cardiovascular adaptations to the pregnancy are intended to accommodate the needs of the maternal-fetal unit they also challenge the maternal circulation system and metabolic homeostasis, thus providing a potential window into a woman's future risk of metabolic and vascular disease (Retnakaran 2009, Romundstad et al. 2010). The incidence of cardiovascular complications for women of child-bearing age is low but a history of preeclampsia or gestational diabetes is known to be associated with cardiovascular risks over decades (Laivuori et al. 1996, Bo et al. 2007). The best way of assessing the future risk during pregnancy is still not known, but numerous studies have been done examining arterial stiffness during pregnancy.

Nevertheless, pregnancy itself has also been shown to have a positive effect on arterial stiffness. Hashimoto et al. examined 2560 women undergoing annual healthcare screening with brachial-ankle PWV and found that women who had 1 or more deliveries had a significantly lower PWV, independent of age and other conventional coronary risk factors

(Hashimoto et al. 2009). They claimed that pregnancy might be a natural endogenous estrogen augmentation or a kind of estrogen "pulse" therapy and this could delay the progress of arteriosclerosis in women.

2.4.1 Changes in normal pregnancy

Arterial stiffness studies during normal pregnancy have revealed that the elasticity in the blood vessels increases during pregnancy as measured by pulse wave velocity (Edouard et al. 1998, Mersich et al. 2005). Spaanderman et al. evaluated local stiffness and compliance in femoral and carotid arteries and determined an increase in elasticity in those vessels already during the very early stages of pregnancy (Spaanderman et al. 2000). Furthermore AIx has been shown to decrease already in between 6 and 7 weeks gestation when this value was compared to the same women prior to conception (Mahendru et al. 2012). In a British study conducted by Macedo et al. AIx declined during pregnancy, reaching its nadir in midpregnancy but there was no significant change in aortic stiffness as measured by PWV (Macedo et al. 2008). An Austrian study group conducted a longitudinal study in 53 healthy pregnant women, and their findings of AIx are seen in figure 6 (Franz et al. 2013). There are also a few other studies indicating that arterial elastic properties may worsen during the 3rd trimester of pregnancy (Robb et al. 2009, Khalil et al. 2009). Higher arterial stiffness in normal pregnancy is known to be associated with lower birth weight and infant catch-up growth in the first 6 months of life, independently of blood pressure (Elvan-Taspinar et al. 2005).

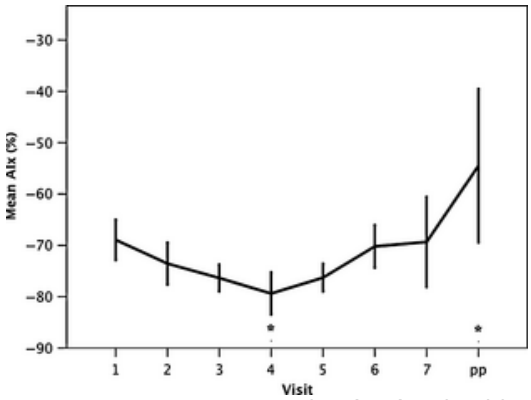


Figure 6. Augmentation index (AIx) in healthy pregnancy. Visits 1–7: continuous measurements during pregnancy, beginning at the 11th week of gestation; pp: measurement at 3–6 months postpartum; error bars: 95% confidence interval; *$p < 0.05$ compared with Visit 1. (With permission from Franz et al. 2013.)

ABPM has been used during pregnancy as a tool for exploring the extensive changes in cardiovascular physiology. In a normal pregnancy, the diurnal blood pressure reduction is believed to be 12-14% in SBP and 18-19% in DBP during sleep (Brown et al. 1998). In an evaluation of the utility of ABPM in pregnant women Walker et al. found out that most women (79%) found that the monitor did disturb their sleep to some degree and 15% of women discontinued monitoring, with sleep disturbance being the strongest predictor of

cessation of use. The researchers proposed that a withdrawal rate of approximately 15% should be considered in ABPM studies in pregnant women (Walker et al. 2004). The possible role of ABPM in predicting transformation from gestational hypertension to preeclampsia has been studied by Davis et al. (Davis et al. 2007). They examined 118 women at the onset of gestational hypertension and discovered that in the women whose gestational hypertension progressed to preeclampsia, the hypertension appeared earlier (33 vs. 37 weeks, $p<0.001$), and they had higher blood pressures, significantly higher awake values and also 24-h pressures, and they were older (30 vs. 33 years, $P=0.035$).

A recent review about ABPM measurements in pregnancy has claimed that the best role for ABPM is to determine whether women with office hypertension in early pregnancy have true (usually essential) hypertension, or white-coat hypertension. In the late postpartum, it has been claimed to have a valuable role in predicting the long-term cardiovascular risk of women with preeclampsia or gestational hypertension (Brown 2013).

2.4.2 Studies of arterial stiffness in gestational hypertension and preeclampsia

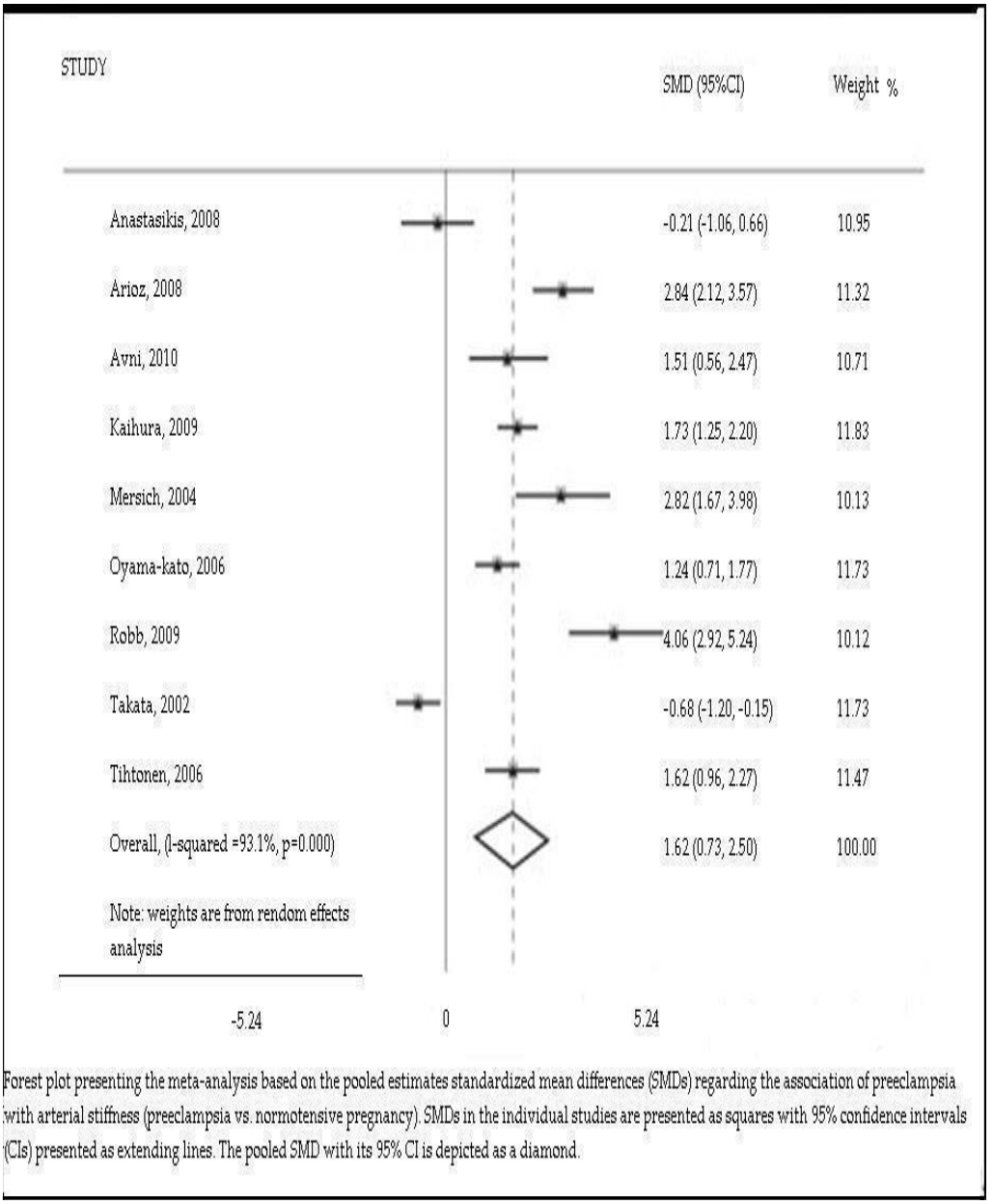
About 15% of all pregnancies are complicated by high blood pressure (James et al. 2004). Hypertensive pregnancies include a wide spectrum of conditions; gestational hypertension, preeclampsia, chronic hypertension and superimposed preeclampsia i.e. preeclampsia in a woman with chronic hypertension, diabetes, or preexisting renal disease or other cardiovascular disorders. The background of preeclampsia is still not totally clear but the most widely accepted hypothesis states that insufficient invasion of the uterine spiral arteries by placental cytotrophoblasts causes placental ischemia which then leads to the release of still unknown vasoactive factors. These substances damage the maternal endothelium causing further impairment of endothelial function and the clinical symptoms hypertension and proteinuria (Steegers et al. 2010). Severe preterm preeclampsia is clearly associated with an underlying placental abnormality, but milder hypertensive conditions near term can exist without there being any placental dysfunction (Vatten et al. 2004, Valensise et al. 2008, Phillips et al. 2010). Preeclampsia has been shown to be associated with reduced plasma volume (Hays et al. 1985) and significant peripheral vasoconstriction (Dennis et al. 2012). Arterial stiffness is increased in hypertensive and preeclamptic pregnancies as assessed by the augmentation index (Ronnback et al. 2005) and PWV (Tihtonen et al. 2006, Kaihura et al. 2009). Tihtonen et al. studied 29 healthy primiparas with uncomplicated pregnancies, 20 with preeclampsia and 18 with chronic hypertension during the third trimester. PWV was 9.6 ± 1.0, 13.8 ± 3.9 and 12.8 ± 2.7 m/s, respectively, $P< 0.0001$. It was found that, the women with chronic hypertension shared a common feature of arterial stiffness, but the changes in these women were less than those present in preeclampsia (Tihtonen et al. 2006). Increased maternal arterial stiffness assessed by pulse wave velocity or pulse wave analysis has been proposed to predate the development of preeclampsia, and thus probably could be used in screening (Khalil et al. 2009b, Savvidou et al. 2011). In addition, endothelial dysfunction is present in hypertensive pregnancies (Germain et al. 2007, Powe et al. 2011).

Preeclampsia has been frequently found to be associated with non-dipping (Brown et al. 2001) and nocturnal hypertension in preeclampsia has been claimed to associate with elevated levels of compounds related to endothelial damage (Bouchlariotou et al. 2008). Arioz et al. found that the stiffness index (SI) was significantly increased in preeclamptic vs. normal pregnancies, but there was no difference in the dipping status between the groups

(Arioz et al. 2008). Ayala et al. analyzed a total of 759 48-h ambulatory blood pressure series in pregnant women every 4 weeks after the first obstetric visit. They stated that the significant differences in blood pressure between healthy and complicated pregnancies could be observed as early as the first trimester of pregnancy and these remained throughout the pregnancy even though the blood pressure variability was well within the normal physiological range IMT (Ayala et al. 1997).

After preeclampsia, the altered arterial properties have also been shown to persist for 6 months, even as long as 3 years after the delivery (Estensen et al. 2013). Spaanderman et al. measured arterial compliance in pregnant women with a history of preeclampsia in a previous pregnancy, during weeks 5 and 7 of their second gestation and stated that the increase in vascular compliance commonly seen during the first trimester of normal pregnancy failed to occur in women with a history of preeclampsia (Spaanderman et al. 2000). A history of preeclampsia was associated with a nearly 4-fold risk of hypertension, more than doubled risk of ischemic heart disease and a nearly doubled risk of stroke and venous thromboembolism (Bellamy et al. 2007). In a Norwegian study, a significantly larger IMT (0.86 mm vs. 0.82 mm, P=0.001) was found in previously preeclamptic women as compared to women with no hypertensive problems in their pregnancies even as long as 25 years after their first pregnancy (Andersgaard et al. 2012).

A recent comprehensive review (Hausvater et al. 2012) examining the association between preeclampsia and arterial stiffness has concluded that: "There is some evidence to suggest the ability of arterial stiffness measurements to predict the onset of preeclampsia. Furthermore, it has been reported that the increased cardiovascular risk observed in women with preeclampsia or with a history of preeclampsia could, in part, occur through increased arterial stiffness." The association between preeclampsia and arterial stiffness described in the review is shown in Figure 7.



Forest plot presenting the meta-analysis based on the pooled estimates standardized mean differences (SMDs) regarding the association of preeclampsia with arterial stiffness (preeclampsia vs. normotensive pregnancy). SMDs in the individual studies are presented as squares with 95% confidence intervals (CIs) presented as extending lines. The pooled SMD with its 95% CI is depicted as a diamond.

Figure 7. The association between preeclampsia and arterial stiffness (With permission from Hausvater et al. 2012.)

2.4.3 Studies of arterial stiffness in gestational diabetes

Gestational diabetes mellitus (GDM) is defined as glucose intolerance with its onset or first recognition during pregnancy and it occurs in Finland in about 8% of pregnancies, in Kuopio University Hospital area nowadays in about 18% of pregnancies 2012 (THL 2012). The prevalence of GDM is continuously increasing, since overweight is one of the major risk factors. GDM is known to be highly associated with gestational hypertension and preeclampsia, these three conditions are sharing many risk factors (Carpenter 2007). The vascular changes in GDM have been studied mainly at the endothelial level (Banerjee et al. 2006). Paradisi et al. used FMD (flow mediated dilation) to reveal that endothelial dysfunction was present in those pregnancies complicated by GDM (Paradisi et al. 2002). Bulzico et al. found no change in aortic stiffness in GDM pregnancies compared to normal pregnancies (Bulzico et al. 2012).

Savvidou et al. (Savvidou et al. 2010) have shown that pregnancies complicated by insulin resistance are associated with maternal arterial stiffness measured by PWV and AIx increasing progressively from controls to gestational to type 2. In that study, the increase in PWV was 10% in GDM and 17% in type 2 diabetes compared to normal pregnancy. The authors claimed that this difference, although small, was likely to be clinically significant. A history of GDM is a significant risk factor for type 2 diabetes (Kim et al. 2002), the prevalence of DM being nearly eightfold among women with prior GDM compared to the non-GDM population during the 10 year follow-up (Chodick et al. 2010). Furthermore, metabolic syndrome and other cardiovascular diseases are more common among women with prior GDM (Sullivan et al. 2012). A history of GDM has also been shown to be a risk for endothelial dysfunction (Bo et al. 2007, Anastasiou et al. 1998) and increased wall stiffness in the common carotid artery (Hu et al. 1998), even after the glucose tolerance has normalized.

2.5 CAROTID ARTERY STUDIES DURING PREGNANCY

Changes in the elastic properties of the carotid artery are thought to be different from those occurring in the aorta during pregnancy, for example, there is one report that the carotid artery stiffens independently of other arterial beds (Visontai et al. 2002). In fact, a Hungarian study described that all the carotid artery elastic parameters adversely affected during a normal pregnancy as a mirror image to the elasticity in the aorta (Mersich et al. 2005). This is shown in figure 8. They studied twelve normotensive pregnant women longitudinally during the three trimesters of pregnancy and 12 weeks postpartum. All carotid artery elastic parameters indicated significant stiffening from first to third trimester (1.8 ± 0.2 vs. 2.9 ± 0.3 mmHg for incremental elastic modulus), which was reversed after delivery (2.3 ± 0.2 mmHg). Aortic PWV decreased during pregnancy (6.2 ± 0.2 versus 5.4 ± 0.2 m/s), showing increased elasticity in aorta, and increased significantly again in the postpartum period (6.7 ± 0.2 m/s). No correlation was found between changes in carotid artery elastic parameters and changes in aortic PWV, i.e. the opposing mechanisms determining aortic and carotid elasticity during pregnancy appear to be unrelated.

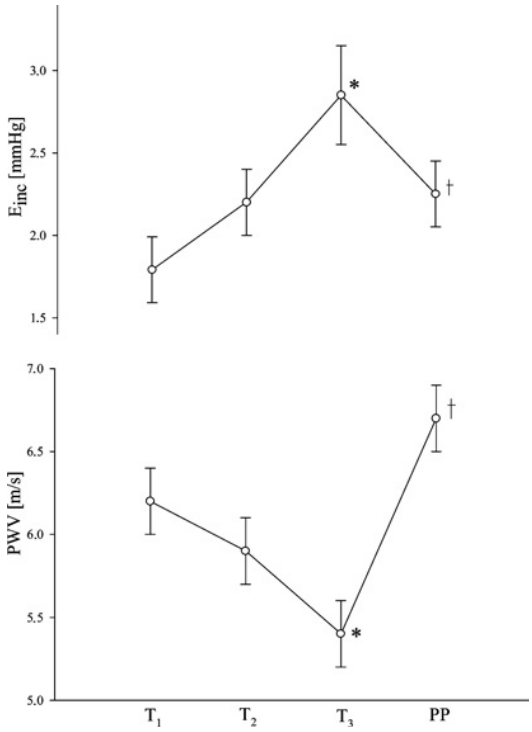


Figure 8. Changes in carotid Einc (incremental modulus of elasticity) and aortic PWV during the three trimesters (T) of pregnancy (T1, T2 and T3 respectively) and PP. ∗=T3 significantly different from T1, P <0.05; †=significantly different from T3, P <0.05. Reproduced with permission from Mersich, Rigó, Besenyei, Lénárd, Studinger and Kollai, (2005), (*Clin.Sci.)* 109, (103-107).©the Biochemical Society

Yuan et al. compared women in their third trimester with non-pregnant women and discovered that the regional carotid arterial stiffness was elevated: PWV in carotid artery was 21% higher and stiffness index was 35% higher in pregnancy group (Yuan et al. 2013b). Furthermore, the diameter of carotid artery was 13% larger than in non-pregnancy group; however, twenty months after delivery all of these parameters had returned to normal.
The same Chinese group compared normal and preeclamptic pregnancies and found that IMT (31% higher), PWV (18% higher) and carotid wall tension (43% higher) all were adversely affected by preeclampsia. AIx was also significantly changed in preeclampsia vs. normal pregnancy (7.9 ± 9.2 vs. -5.0 ± 5.6, P< 0.0001) The authors postulated that, in addition to the vasoconstriction of smaller peripheral arteries, abnormal arterial remodeling and disturbed vascular mechanics occur in the larger elastic arteries in preeclampsia (Yuan et al. 2013a). Furthermore, these changes were still evident eighteen months after delivery. Also Ma et al. found increased common carotid artery stiffness in preeclamptic women compared to normotensive pregnant women (Ma et al. 2012).

3 Aims of the study

The overall aim of this study was to assess arterial stiffness in normal and complicated pregnancies. Firstly it was decided to evaluate the normal range of AASI during pregnancy and postpartum by measuring AASI in uncomplicated singleton and twin pregnancies. Secondly it was hypothesized that in pregnancies complicated by gestational diabetes or hypertension/preeclampsia, arterial stiffness assessed by AASI would be increased as compared to normal pregnancies. Furthermore, the nocturnal dipping status in hypertensive vs. normal pregnancies was evaluated. Thirdly, the effect of pregnancy on carotid artery elasticity was examined. The individual aims were to determine:

1. AASI in uncomplicated singleton and twin pregnancies.

2. The changes in vascular function, primarily AASI, and in lipid values in the third trimester and three months postpartum in normal pregnancies vs. GDM pregnancies.

3. The changes in AASI and nocturnal blood pressure fall (dipping) and metabolism in normal pregnancies vs. pregnancies complicated by gestational hypertension or preeclampsia.

4. The effect of pregnancy on carotid artery elasticity and the associations between metabolic factors, endothelial function and carotid arterial elasticity.

4 Materials and methods

4.1 PATIENTS IN STUDIES I-III

A total of 123 women in their third pregnancy trimester were recruited from the Kuopio University Hospital maternity clinic or the antenatal department for the Complicated Pregnancy Study during the years 2002-2007. The subgroups are presented in Figure 9. All consecutive affected pregnant patients were eligible. The cohort itself was a convenience sample so that the cases were recruited during the years 2002-2007 from the Kuopio University Hospital after they had been admitted to the antenatal department or were being followed at the outpatient clinic. They were requested to participate and enrolled into the study if they were otherwise healthy, their clinical condition was stable enough to adhere to the protocol and if adequate research resources, including personal, were available at the time of enrolment. Smokers and pregnancies with fetal anomalies were excluded. Controls were matched for pregnancy weeks and selected from women with uncomplicated pregnancies seen at the maternity clinic for different reasons. Their pregnancy was deemed to be normal after the checkup.

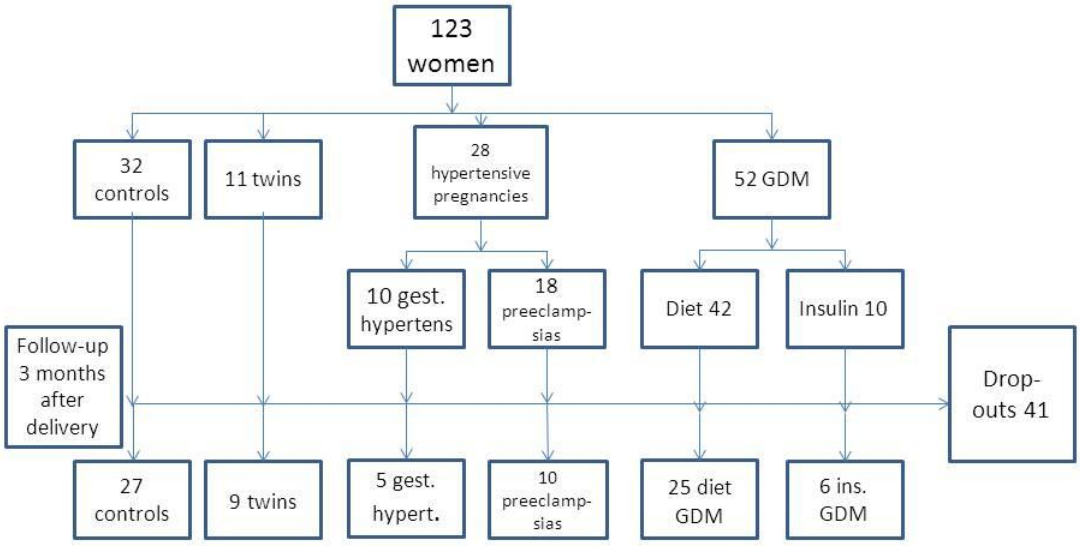


Figure 9. Subgroups and numbers of women in The Complicated Pregnancy Study

Gestational hypertension was defined as a systolic blood pressure level ≥ 140 mmHg or a diastolic blood pressure level ≥ 90 mmHg in two separate measurements after 20 weeks of pregnancy in women with previously normal blood pressure. Preeclampsia was defined as hypertension and proteinuria ≥ 300 mg over 24 hours. If blood pressure was over 160/100mmHg or the patient had symptoms like headache, antihypertensive medication (primarily labetalol) was started. At the time of examinations during pregnancy, 16 of 28 hypertensive/preeclamptic patients were being treated with antihypertensive medication
Gestational diabetes was determined as an abnormal 75 g oral glucose test (OGTT) performed in pregnancy weeks 26-28. In 2002-2007, the normal values for pregnant women were lower than 4.8-11.2-9.9 mmol/l (fasting- 1h- 2h). Of the GDM women 91.7% had fasting glucose higher than the reference value, 27.7% had the 1-h value and 4.3% had the 2-h value higher than the reference value. Women with GDM received structured dietary and exercise advice and were taught home blood glucose monitoring by a diabetes specialist nurse. The recommendation was to measure fasting blood glucose in the morning and postprandial glucose levels 1 h after a meal. If there were values over the limits (fasting glucose >6.0 mmol/l and postprandial >7.5mmol/l) despite nutritional advice and exercise, then insulin-therapy was initiated.

4.2 POPULATION AND DATABASE IN STUDY IV

The Cardiovascular Risk in Young Finns Study is an ongoing prospective population-based 5-centre follow-up study of atherosclerosis risk factors in Finnish children and adolescents. The first cross-sectional survey was conducted in 1980 in 3596 children randomly chosen from a national register and aged 3, 6, 9, 12, 15 and 18 years (Åkerblom et al. 1985). In 2001, 2283 of these individuals were re-examined when they were aged 24-39 years. Since one aim was to examine the influence of pregnancy on carotid artery elasticity, we focused on the pregnant women. Out of the sample, 62 of the participants were pregnant women and 62 non-pregnant women matched for age and smoking status were chosen as controls. In 2007, there were 37 pregnant women among 2204 participants and 37 matched women were chosen as controls. In both 2001 and 2007 11% of women in both pregnant and control groups were smokers and 89% were non-smokers. A total of nine women from the year 2007 sample had also been examined in 2001, three of them being pregnant on both occasions, three of them being pregnant once and three of them being controls on both times. Thus, there were 99 pregnant women and 99 controls in our study: 33 women (33.3%) in first trimester (T1, ≤ 15 weeks), 32 women (32.3%) in second (T2, 16-28 weeks) and 29 women (29.3) in the third trimester (T3, ≥29 weeks). The gestational data was not available for 5 women (5.1%). The mean gestational age (±SD) was 22±10 weeks. The numbers of subjects are seen in Table 3.

Table 3. The subjects in the Cardiovascular Risk in Young Finns Study

Study group	Non-pregnant	1. trimester ≤ 15 weeks	2. trimester 16-28weeks	3. trimester ≥ 29 weeks
Number of women	99	33	32	29

4.3 METHODS

4.3.1 Anthropometry and Physiology

In both, the Complicated Pregnancy Study and the Cardiovascular Risk in Young Finns Study, the height and weight were measured. Office blood pressure was determined in the Complicated Pregnancy Study with Mercurius 300 sphygmomanometer (Speider & Keller, Jungingen, Germany) and in the Cardiovascular Risk in Young Finns study with a random zero sphygmomanometer (Hawksley & Sons Ltd, Lancin, UK), while the patient was seated after 5 minutes rest. The cuff was placed in the non-dominant arm at the brachial level. The average of three blood pressure measurements was used in the analysis.

In the Complicated Pregnancy Study, in all subjects, both during and after pregnancy, maternal electrocardiography (ECG) and non-invasive beat-to-beat arterial blood pressure were recorded for 5 minutes at rest and twenty-four-hour ambulatory ECG, autonomic nervous system assessment and body composition analysis by bioimpedance were made, although the data were not used in these analysis.

4.3.2 Blood and urine samples

In the Complicated Pregnancy Study, overnight fasting blood samples were acquired for laboratory measurements during last trimester and 3 months after delivery. Samples were centrifuged at 2 000g for 10 minutes and serum or plasma were separated. The concentrations of plasma glucose and serum lipids and IL-6 were determined. In preeclamptic and hypertensive pregnancies, also uric acid, lactate dehydrogenase, alanine aminotransferase and creatinine were determined as a part of clinical routine and there was analysis of urine. This was first performed by a dipstick measurement and if positive, then a 24-h urine sample was collected.

In the Cardiovascular Risk in Young Finns Study, venous blood samples were drawn after an overnight fast for determination of serum lipoprotein levels.

4.3.2.1 Glucose

In the Complicated Pregnancy Study, plasma glucose levels were determined by the hexokinase method (Konelab 60i Clinical Chemistry Analyzer, Thermo Electron Co, Finland).

4.3.2.2 Serum lipid concentrations

In the Complicated Pregnancy Study, all lipid analyses were performed by standard methods with Konelab 60i Clinical Chemistry Analyzer (Thermo Electron Co, Finland). The triglyceride concentration was determined by GPO-PAP enzymatic, photometric assay (Konelab TRIGLYCERIDES kit, Thermo Electron Co, Finland) and the total serum cholesterol concentration was analysed by an enzymatic, photometric assay (Konelab CHOLESTEROL kit, Thermo Electron Co, Finland). Concentrations of high density

lipoprotein (HDL)-cholesterol and low-density lipoprotein (LDL)-cholesterol were determined by a direct, enzymatic, photometric method (Konelab HDL-CHOLESTEROL and Konelab LDL-CHOLESTEROL kits, Thermo Electron Co, Finland).

In the Cardiovascular Risk in Young Finns Study the lipids were determined enzymatically as previously described in the article of Juonala et al. (Juonala et al. 2005).

4.3.2.3 Interleukin-6 analysis

Interleukin-6 (IL-6) concentrations were measured with a commercially available solid-phase enzyme-linked immunosorbent assay (ELISA) according to the protocol supplied by the manufacturer (Quantikine HS Human IL-6 Kit, R&D Systems, Minneapolis, USA). The working range was 0.156–10 pg/ml for IL-6. Calibrators for IL-6 assays were analyzed in duplicate but the samples were assayed as single measurements. The absorbances in ELISA tests were measured at a wavelength of 490 nm using a microplate reader (Tecan SPECTRAFluor, Tecan Group Ltd., Maennedorf, Switzerland).

4.3.2.4 Insulin analysis and assessment of HOMA-IR

Serum insulin was measured by the electrochemiluminescence immunoassay method (Cobas 6000 analyzer, Hitachi High Technology Co, Tokyo, Japan). The homeostasis model assessment of insulin resistance (HOMA-IR) was used to estimate the levels of insulin resistance with the equation: HOMA-IR= fasting insulin (mU/l × fasting glucose (mmol/l)/22.5 (Matthews et al. 1985).

4.3.2.5 Serum uric acid, lactate dehydrogenase, alanine aminotransferase and creatinine

From serum samples, the creatinine concentration was measured by the Jaffe kinetic method, the uric acid concentration was measured by enzymatic uricase-peroxidase assay, the alanine aminotransferase concentration was measured by the kinetic IFCC method with pyridoxal phosphate addition and the lactate dehydrogenase concentration was assayed by the kinetic IFCC method.

4.3.3 Ambulatory blood pressure measurements and assessment of AASI and dipping

In the Complicated Pregnancy Study twenty-four-hour ambulatory blood pressure measurements were conducted using an ambulatory blood pressure system (SpaceLabs 90207; SpaceLabs Medical, Inc., Redmond, Washington, USA). The cuff was placed in the nondominant arm at the brachial level. We programmed the recorders to take blood pressure readings at 15- minute intervals during the daytime and every 30-minutes during the night-time. The duration of night-time was defined individually for each participant according to their normal rhythm. AASI was calculated as 1 minus the regression slope diastolic blood pressure values plotted against systolic pressures obtained from individual twenty-four-hour monitoring. The slope was not forced through the origin.

The nocturnal blood pressure fall was defined as the difference between individual daytime and night-time values of systolic and diastolic pressures, respectively, i.e. SBP^{day}-SBP^{night}= systolic dipping and DBP^{day}-DBP^{night}= diastolic dipping. In our study, individuals with nocturnal systolic blood pressure less than 10 mmHg lower than their values daytime were defined as nondippers.

4.3.4 Ultrasound studies

Ultrasound studies were performed using Sequoia 512 ultrasound mainframes (Acuson, CA, USA) with 13.0 MHz linear array transducers. Left carotid artery was scanned following a standardized protocol. The intima-media thickness (IMT) was measured as previously described (Raitakari et al. 2003).

4.3.4.1 Carotid artery studies

In the Cardiovascular Risk in Young Finns Study, the assessment of carotid artery elasticity indexes was conducted by the method previously described by Juonala et al. (Juonala et al. 2005). The best quality cardiac cycle was selected from the 5-second clip images. The common carotid diameter 10 mm from carotid bifurcation was measured from the B-mode images using ultrasonic calipers at least twice in end-diastole and end-systole, respectively. The mean of the measurements was used as the end-diastolic and end-systolic diameter.

The assessment of carotid artery is shown in Figure 10. Ultrasound and concomitant brachial blood pressure measurements were used to calculate the indexes of arterial elasticity. Blood pressure was measured just before and immediately after carotid artery ultrasound scanning. In the calculation, mean of these values was used; the formulas are seen in Table 4. Young's Elastic Modulus (YEM) gives an estimate of arterial stiffness that is independent of wall (intima-media) thickness (Riley et al. 1992). Carotid artery distensibility (CAD) measures the ability of the arteries to expand in response to the pulse pressure caused by cardiac contraction and relaxation. Stiffness index (SI) is considered to be relatively independent of blood pressure (Hirai et al. 1989).

Table 4. The variables measured in common carotid artery in Study IV.

Variable	Formula	Characteristics
Young's elastic modulus (YEM)	([SBP – DBP] x diastolic diameter)/([systolic diameter – diastolic diameter] x IMT)	Independent of wall (intima-media) thickness
Carotid artery distensibility (CAD)	([systolic diameter – diastolic diameter]/diastolic diameter)/(SBP – DBP)	Measures the ability of the arteries to expand in response to the PP caused by cardiac contraction and relaxation
Stiffness index (SI)	ln (SBP/DBP)/([systolic diameter – diastolic diameter]/diastolic diameter)	Relatively independent of blood pressure
Intima media thickness (IMT)	The distance between lumen intima and media-adventitia	Shows the grade of arteriosclerosis
Flow mediated dilation (FMD)	The increase in vessel diameter after reactive hyperemia	The dilatation response for increased flow is mainly mediated by nitric oxide release
Carotis communis diameter (CCD)	The distance between lumen-intima interfaces	Associated with cardiovascular risk factor

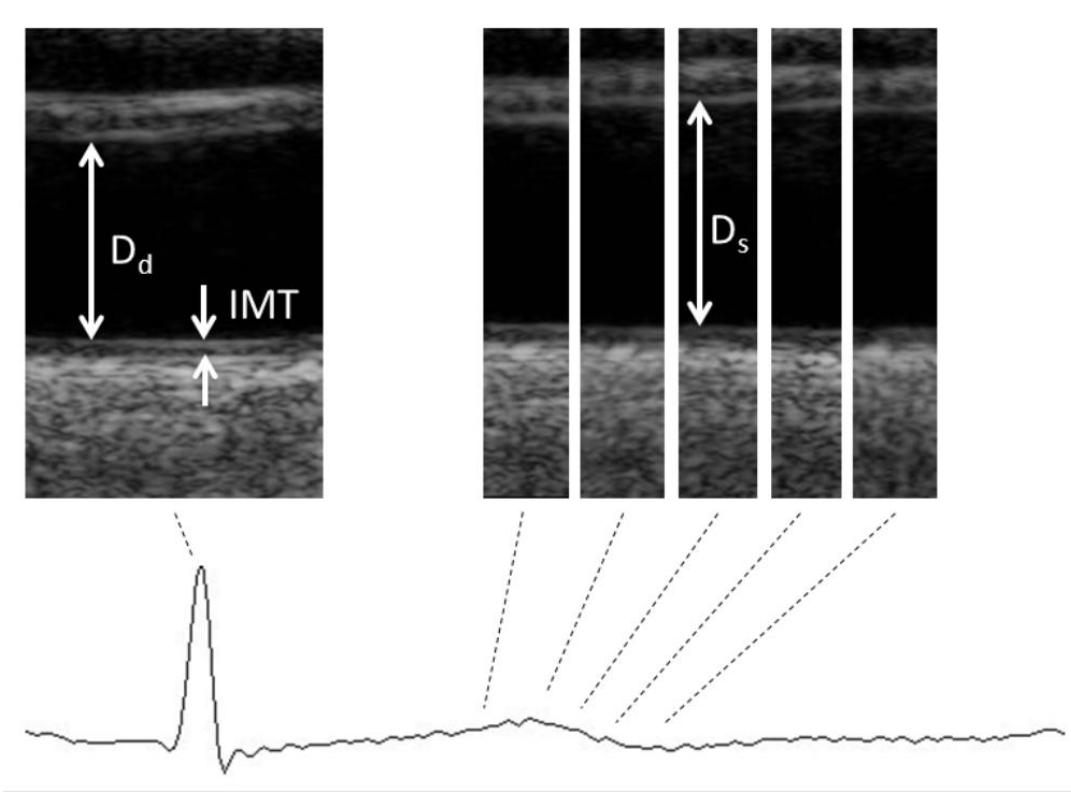


Figure 10. Assessment of common carotid artery diastolic (Dd) and systolic (Ds) diameters and IMT. For measurements of Dd and IMT an ultrasound frame incident with the R-wave on a continuously recorded electrocardiogram was selected. For Ds measurement a frame with the largest diameter was selected.

4.3.4.2 Flow mediated dilation (FMD)

In both studies, the assessment of brachial FMD, the left brachial artery diameter was measured both at rest and after reactive hyperemia. Increased flow was induced by inflation of a pneumatic tourniquet placed around the forearm to a pressure of 250 mmHg for 4.5 min, followed by release. Three measurements of arterial diameter were performed at end-diastole at a fixed distance from an anatomic marker, first at rest and then at 40, 60, and 80 s after cuff release. The vessel diameter in the scans after reactive hyperemia was expressed as the change in absolute diameter (FMD) and as the percentage relative to the resting scan (FMD%) (Juonala et al. 2004).

4.3.5 Statistical analysis

All data management and analyses were carried out using SPSS for Windows on a standard PC. The normality of the distribution of the data was examined with the Kolmogorow-Smirnov- test. Differences between groups were analyzed with the Mann-Whitney U-test or Student t-test or with Kruskal-Wallis-test according to the normality of the distribution. Paired t-test and ANOVA with Bonferroni's post-tests were used in normally distributed variables analyzing changes during vs. after pregnancy. Relationships among variables were assessed by using Pearson's correlation coefficient. In study II, a generalized linear model was used and BMI used as a covariate. Stepwise multivariate analysis with linear regression was used to determine independent predictors of SI, YEM and CAD in the study IV. The results are expressed as means ± SD of the mean. Differences were considered significant if p was < 0.05.

4.3.6. Ethical considerations

The Complicated Pregnancy study was approved by the Ethics Committee of Kuopio University Hospital. The Cardiovascular Risk in Young Finns Study was approved by The Ethics Committee of the Hospital District of Southwest Finland. In both studies, participants provided written informed consent.

5 Results

The clinical characteristics of the subjects in studies I-III are shown in Table 5. As shown in Table 5, the subjects in the different groups were of similar age and had statistically similar maternal heights. Women with GDM and hypertensive pregnancies had higher BMI values than the other groups, but they gained weight during pregnancy similarly to other groups. Birth weights were lower in twins and in hypertensive pregnancies, but they also gave birth slightly earlier than other groups.

Table 5. The study subjects in studies I-III

Variable ± SD	**Controls N=32**	**Twins N= 11**	**GDM (diet) N= 42**	**GDM (ins.) N=10**	**Hyperten-sive N= 10**	**Preeclamp-sia N= 18**
Age (years)	31.2 ± 4.7	29.8 ±3.6 NS	30.5 ± 5.6 NS	32.8 ± 7.6 NS	32.7 ± 5.1 NS	30.4 ±5.9 NS
Height (cm)	166.4 ± 6.8	163.2 ± 3.2 NS	165.3 ± 5.7 NS	165.4 ± 4.5 NS	166.6 ± 5.7 NS	162.4 ± 6.7 NS
Weight before pregnancy (kg)	63.4 ± 7.8	60.7 ±6.3 NS	76.2 ± 16.2 P <0.001	84.4 ± 21.3 P= 0.014	70.9 ± 12.2 NS	64.4 ± 11.6 NS
BMI before pregnancy (kg/m²)	22.9 ± 2.9	22.8 ± 2.2 NS	27.9 ± 5.5 P <0.001	30.9 ± 8.3 P= 0.016	25.5 ± 3.8 P= 0.048	24.4 ± 4.0 NS
Weight gain (kg)	12.8 ± 3.2	16.5 ± 5.5 P= 0.021	12.9 ± 5.5 NS	11.5 ± 6.3 NS	12.2 ± 6.6 NS	16.7 ± 5.7 P= 0.033
Weight 3 months after delivery (kg)	63.9 ± 8.3 NS	64.4 ± 7.4 NS	78.0 ± 14.8 P= 0.002	81.5 ± 8.3 P= 0.027	73.6 ± 13.2 NS	72.9 ± 15.1 NS
Gestational age at birth(weeks)	40.1 ± 0.5	36.4 ± 3.5 P <0.001	40.0 ± 1.5 NS	39.1 ± 1.5 NS	38.3 ± 1.5 P= 0.021	36.9 ± 1.4 P <0.001
Systolic BP office (mmHg)	109.1 ± 7.5	115 ± 10.5 P= 0.049	112.7 ±10.4 NS	116.5 ±15.9 NS	130.9 ±12.7 P <0.001	135.9 ± 9.5 P <0.001
Diastolic BP office (mmHg)	68.9 ± 6.3	71.3 ± 8.8 NS	70.1 ± 9.0 NS	75.0 ± 7.8 P= 0.014	87.7 ± 11.9 P <0.001	89.4 ± 5.5 P <0.001
Birthweight (g)	3597 ±508	2496 ± 566 P <0.001	3793 ± 480 NS	3713 ± 560 NS	3112 ± 564 P= 0.018	2754 ± 533 P <0.001

NS = no significant difference.

The results of ambulatory blood pressure measurements in studies I-III are seen in Table 6. Overall AASI was similar between the controls and study groups with the exception that

GDM women on insulin had higher AASI after pregnancy than the controls. In the women suffering from preeclampsia, both diastolic and systolic dippings were significantly smaller than in the control group, but three months after delivery, there was no difference anymore. The women expecting twins tended to have lower diastolic dipping than women in the control group.

Table 6. AASI and dipping during and after normal and complicated pregnancies. P-values below the measurement results are based on the comparison to the control group, whereas the effect of pregnancy within each group is indicated on a separate line.

	Controls N=32	**Twins N= 11**	**GDM (diet) N= 42**	**GDM (ins.) N=10**	**Hyperten-sive N= 10**	**Preeclamp-sia N= 18**
AASI during pregnancy	0.22 ± 0.13	0.22 ± 0.17 NS	0.23 ± 0.12 NS	0.29 ± 0.21 NS	0.21 ± 0.10 NS	0.27 ± 0.12 NS
AASI after pregnancy	0.21 ± 0.13	0.22 ± 0.18 NS	0.17 ± 0.09 NS	0.33 ± 0.09 P=0.047	0.30 ± 0.13 NS	0.22 ± 0.19 NS
Effect of pregnancy	NS	NS	P=0.002	NS	NS	NS
Syst. dipping during pregnancy (mmHg)	10.5 ± 4.3	7.3 ± 5.4 P=0.053	12.6 ± 5.7 NS	9.1 ± 5.3 NS	9.2 ± 4.6 NS	5.8 ± 8.7 P=0.007
Syst. dipping after pregnancy (mmHg)	9.4 ± 5.3	12.0 ± 5.2 NS	11.8 ± 5.8 NS	8.2 ± 5.6 NS	9.8 ± 4.8 NS	9.4 ± 5.0 NS
Effect of pregnancy	NS	0.011	NS	NS	NS	NS
Diast. dipping during pregnancy (mmHg)	12.6 ± 3.8	9.5 ± 5.2 P=0.046	13.6 ± 4.7 NS	10.4 ± 5.9 NS	9.8 ± 3.7 P=0.070	6.8 ± 6.5 P<0.001
Diast. dipping after pregnancy (mmHg)	10.6 ± 4.2	13.7 ± 5.6 NS	12.8 ± 5.0 NS	8.7 ± 3.9 NS	10.0 ± 2.5 NS	10.7 ± 5.3 NS
Effect of pregnancy	0.006	0.033	NS	NS	NS	NS

NS = no significant difference.

5.1 HEMODYNAMICS AND METABOLISM IN NORMAL AND COMPLICATED PREGNANCIES

In an uncomplicated singleton pregnancy, the systolic blood pressure was 5%, heart rate 5%, total cholesterol 45%, HDL 25%, LDL 57% and triglycerides 336% higher and fasting glucose 8% lower than three months after pregnancy. In the twin pregnancy group, the changes were 8%, 20%, 43% 25%, 49%, 290% and 14 %, respectively. When comparing singletons to the twin group, the systolic daytime pressure and systolic and diastolic night-time pressures were significantly higher in twin pregnancies

Women in both GDM groups had significantly higher glucose and HOMA-IR values during pregnancy. Three months after pregnancy, lipid values were less favourable in both GDM groups than in the controls, but after adjustment for BMI, only glucose metabolism and LDL-values remained significantly worse in both GDM groups. In the insulin GDM group, blood pressures were significantly higher both during pregnancy and after delivery. In the pooled gestational hypertension/preeclampsia group, the values of LDL (P=0.048), creatinine (P=0.018) and triglycerides (P=0.001) were higher than in the control group. After pregnancy, the complicated group still had higher triglyceride levels (0.7 ± 0.4 vs. 1.1 ± 0.6, P= 0.008). Accordingly, all blood pressures were still higher in the pooled hypertensive/preeclampsia group 3 months after pregnancy (P<0.001). During pregnancy, interleukin-6 concentrations were significantly higher in the preeclamptic group when compared to the normotensive group (3.06 ± 2.34 vs. 1.96 ± 1.29 pmol/l, P= 0.034). Three months after delivery, the IL-6 levels had declined in the preeclampsia group to 1.60 ± 1.17 pmol/l (P=0.01). Interestingly, in the pooled hypertension/preeclampsia group the interleukin-6 concentration correlated positively with nocturnal mean arterial pressure (r=0.497, P=0.010).

5.2 AMBULATORY ARTERIAL STIFFNESS INDEX IN NORMAL AND COMPLICATED PREGNANCIES

Normal uncomplicated singleton or twin pregnancy had no detectable effects on AASI. AASI during pregnancy correlated directly with maternal BMI in normal pregnancies (r= 0.366, P= 0.016). AASI after pregnancy correlated with maternal age (r= 0.440, P= 0.009), with systolic (r= -0.536, P=0.001) and diastolic (r= -0.674, P< 0.0001) dipping and with postpartum HDL (r= -0.363, P= 0.038) in normal pregnancies.

AASI increased and was significantly higher in women needing insulin three months after delivery being 94% higher than in GDM women on diet (P= 0.001) and 57% higher than in the control women. In the diet GDM group, AASI was 26% lower after delivery, the direction being opposite to that found in the insulin group. In the GDM study, AASI correlated with maternal age, BMI, strongly with night-time pressures and inversely with dippings. The AASI slopes of one woman in the GDM group are shown in Figure 11.

In the pooled hypertensive/preeclampsia group, AASI correlated inversely with BMI (r=-0.395, P=0.042) and weight before pregnancy(r= -0.491, P=0.009), the correlation being opposite to that found in the other groups. AASI during pregnancy also correlated with renal function after delivery (creatinine (r=0.765, p=0.004), glomerular filtration rate (r=-0.584, p=0.046)). AASI assessed after pregnancy correlated inversely with both postpartum

systolic and diastolic nocturnal dipping and with fasting glucose values during pregnancy and total cholesterol level after pregnancy.

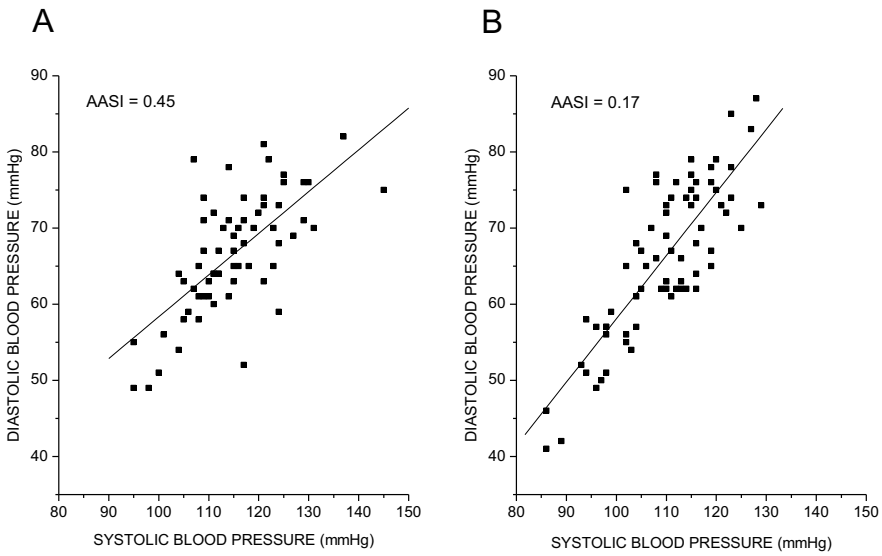


Figure 11. The 24-h ABPM values of one woman with GDM on diet: A= during pregnancy, B= 3 months after delivery. AASI is calculated as 1 - the slope.

5.3 NOCTURNAL BLOOD PRESSURE DIPPING IN NORMAL AND COMPLICATED PREGNANCIES

In both uncomplicated singleton and twin pregnancy groups, the nocturnal diastolic dipping was significantly different compared to postpartum, but inversely; in singleton pregnancies, dipping was greater during pregnancy and in twin pregnancies it was smaller. The nocturnal dipping during pregnancy was smaller in women expecting twins (P=0.046-0.053).

In the GDM pregnancies, there were no significant differences in dippings compared with the control group and the dipping patterns were similar.

In the pooled hypertensive/preeclampsia group, both systolic (7 ± 8 vs. 11 ± 4, p=0.031) and diastolic (8 ± 6 vs. 13 ± 4, P<0.001) dippings were significantly smaller than in the control group, recovering to the same level as in the controls after pregnancy. In this group, the lack of nocturnal dipping also correlated positively with the interleukin- 6 level. When the hypertensive/preeclampsia group was pooled with controls, nondippers had a higher creatinine level during pregnancy, although the creatinine values were within the normal range (64.3 ± 12.6 mmol/l vs. 51.3 ± 7.0 mmol/l, P= 0.007).

The diurnal variations of two study individuals are shown in Figure 12.

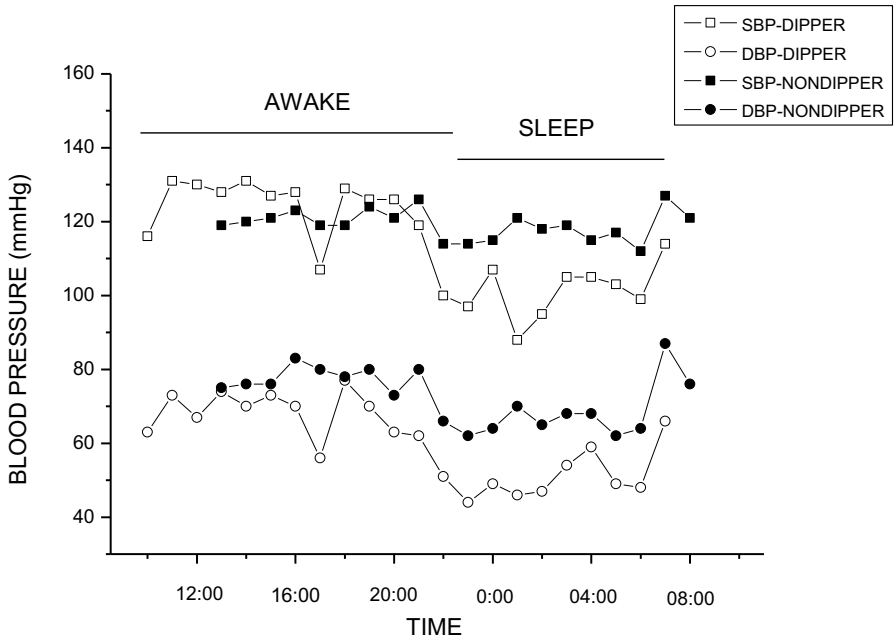


Figure 12. The 24-h ambulatory blood pressure measurements from two different individuals in the Complicated Pregnancy Study

5.4 CAROTID ARTERY ELASTICITY DURING PREGNANCY

The elasticity indexes were studied in the Cardiovascular Risk in Young Finns Study. There was no information on the potential preexisting disorders or any pregnancy complications in these women, only gestational weeks and smoking status were recorded. The results subdivided according to pregnancy trimesters are shown in Table 7. SI was 57 % and YEM was 75% higher and CAD 36% lower in the third trimester group as compared to the first trimester group. The diameter of the common carotid artery grew by 9% and the diameter of brachial artery by 7% when the first and third trimesters were compared. FMD% displayed significant increase from the first to the third trimester only after adjusting with baseline brachial artery diameter; P=0.033 for linearity between the three trimesters and P= 0.009 between all the groups. The bivariate correlation analysis revealed significant correlations between carotid elasticity indexes and maternal age, weight, lipids and systolic and diastolic blood pressure but in the stepwise multivariate analysis, only gestational age correlated independently with all these indexes. The visualization of carotid artery with ultrasound and the timing of diastolic and systolic diameter measurements are shown in Figure 10 on the page 28.

Table 7. The elasticity of carotid artery measured in Study IV

Variable ± SD	**Non-pregnant (N=99)**	**First trimester (N=33)**	**Second trimester (N=32)**	**Third trimester (N=29)**	**P-value between all the groups**	**P-value between the three trimesters**
SI	5.50 ± 2.44	5.15 ±1.67	6.47 ± 2.34	8.07 ± 3.13	<0.001	<0.001
YEM (mmHg/mm)	900 ± 439	805 ± 278	1030 ± 428	1412 ± 695	0.001	<0.001
CAD (%/10mmHg)	2.24 ± 0.87	2.43 ±0.82	1.99 ± 0.84	1.56 ± 0.59	<0.001	<0.001
CCD (mm)	5.42 ± 0.42	5.39 ±0.40	5.60 ± 0.44	5.87 ± 0.50	<0.001	<0.001
IMT (mm)	0.58 ± 0.08	0.57 ±0.08	0.56 ± 0.08	0.55 ± 0.07	0.160	0.488
FMD%	10.02 ±4.41	9.56 ±4.54	9.99 ± 4.90	10.23 ±5.22	0.880	0.883
BBD (mm)	3.03 ± 0.32	3.05 ±0.29	3.25 ± 0.25	3.27 ± 0.33	<0.001	<0.001

6 Discussion

The compliance and resistance of arteries are phenomena crucial for the human body to adapt to different situations and conditions such as pregnancy. Arterial stiffness is known to be associated with increased cardiovascular risk and it is a target of growing research efforts and clinical studies. A method to assess arterial stiffness easily and as a part of normal clinical practice would be useful. This was also the goal of Dolan et al., when they proposed the concept of AASI and they first published their findings in 2006 (Dolan et al. 2006a). Since then, it has been discussed in detail; many arguments have been stated both for and against its clinical validity.

In the Complicated Pregnancy Study, ambulatory blood pressure measurements were done and in 2007 when the data collection was finished, AASI was a new, recently published and promising index to assess arterial stiffness. Furthermore, AASI was easily accessible from the individual ABPM values. Our aim was to find out how pregnancy and pregnancy complications would affect AASI. It was speculated that AASI could be a useful method, for example to screen and identify pregnant women who would develop preeclampsia later. In addition, the non-pregnant reference for each woman was available three months after a normal, gestational diabetic or hypertensive pregnancy. Therefore, it was hoped to clarify the metabolic situation three months after a complicated pregnancy and to determine the consequences in maternal health.

Nocturnal dipping is closely related to AASI in previous studies and that connection was confirmed here; this led us to focus also on nocturnal dipping.

In pregnant women, AASI, and FMD from previous studies, (Saarelainen et al. 2012) showed quite different results from each other. Therefore it was necessary to compare AASI to carotid artery stiffness representing local rather than the whole artery tree stiffness with the data gathered from the Cardiovascular Risk in Young Finns Study.

6.1 THE MAIN FINDINGS

The main findings of studies I-IV are listed in Table 8.

Table 8. The main results and other findings of studies I-IV.

Study	Main result	Other findings
I	Normal singleton or twin pregnancy had no effect on AASI	AASI during pregnancy correlated with BMI before pregnancy AASI after pregnancy correlated with nocturnal dipping and maternal age
II	In GDM women on diet AASI decreased after delivery In GDM women requiring insulin AASI after delivery was significantly higher than in the other groups	GDM women had more adverse lipid profile and higher blood glucose after pregnancy, the profile being worst in GDM requiring insulin
III	Hypertensive/preeclamptic pregnancy had no effect on AASI Preeclamptic women had a flattened dipping profile during pregnancy	Higher AASI predicted signs of postpartum metabolic syndrome
IV	Carotid artery elasticity, measured by SI, YEM and CAD, declined towards the end of the pregnancy	No association between maternal hyperlipidemia or FMD and decreasing elasticity

An uncomplicated singleton or twin pregnancy had no effect on AASI, probably because the women were young and healthy. The only group in which there was a significant change in AASI from pregnancy to postpartum was the GDM diet group. Their AASI values at 3 months after pregnancy decreased by 26% to 0.17, the lowest of the whole study, although their glucose and lipid values and BMIs were higher than in the control group. One can speculate that in these women, with a mild GDM with no medical intervention apart from exercise and diet, through "the window to woman's later life", (Retnakaran 2009) it was possible to observe the arterial stiffening destined to shape her cardiovasculature outlook in the future. The change was seen despite the prudent diet they were committed to during pregnancy but not postpartum. The relapse into their pre-pregnancy lifestyle was reflected in the fact that the lipid profiles during pregnancy, but not postpartum, were similar to or even better in the GDM group than in the control one. Accordingly, the weight gain during, but not after pregnancy, was similar in both groups. Over the years following the index pregnancy, women with a history of GDM are known to display an enhanced cardiovascular risk profile and an increased incidence of cardiovascular diseases (Sullivan et al. 2012).

AASI increased significantly after pregnancy in the GDM women who needed insulin to control the glucose values and in the gestational hypertension group. The GDM women using insulin have clusters of even more serious cardiovascular risk factors (Barden et al. 2013) and their risk surfaced after insulin medication was terminated. Accordingly, women with gestational hypertension are known to be at risk of suffering later cardiovascular complications (Garovic et al. 2010, Männistö et al. 2013); and in our study, in most of these cases, the antihypertensive medication was stopped after the delivery. In this group, however, it was possible to identify an insignificant increase of AASI. One can speculate that in these two groups, the termination of the medication resulted in a return, even an increase in arterial stiffness, a fact noted at three months postpartum.

Preeclampsia is a somewhat different disease from gestational hypertension, with the latter developing more slowly and being less intense. This difference could explain the contradictory changes in AASI in these two groups after delivery. Preeclampsia is known to be associated with abnormal placental function, starting in impaired development of the villous arteries. In preeclampsia, the inflammatory reaction is more intense and acute; frequently the antihypertensive medication is not started at all, but the delivery is induced or a caesarean section is done. One can try to explain that the tendency of AASI to decrease after giving birth in the preeclampsia group may be due to the decrease in arterial inflammation (Makkonen et al. 2002). The flattened nocturnal dipping was strongly associated with increased interleukin-6 levels in preeclamptic pregnancies as evidence of endothelial damage.

The decrease in carotid artery elasticity was not dependent on the maternal hyperlipidemia or the diameter of the carotid artery. Furthermore, it was not mediated through pregnancy-related changes in endothelial function. The reasons for the decreasing elasticity in carotid arteries are not known. The distensability of other arteries during pregnancy functions very differently from the carotid arteries. One possible explanation is the existence of some kind of preserving effect where the pregnancy-related increases in cardiac output and blood volume with probable unfavorable effects on brain perfusion are kept under control through regulated carotid artery compliance. According to this hypothesis, a local decrease in carotid artery elasticity may actually be an appropriate adaptation to pregnancy hemodynamics. Visontai et al. have speculated that there could be fewer estrogen receptors in carotid arteries, and this might explain the difference in its elasticity from the other arteries during pregnancy (Visontai et al. 2002).

6.2 FINDINGS IN RELATION TO OTHER STUDIES

There is significant evidence indicating that the elasticity in arteries increases during normal pregnancy and it is present already in the first trimester. These present results are not in line with studies, where enhanced elasticity was measured by PWV (Edouard et al. 1998, Mersich et al. 2005) and AIx (Mahendru et al. 2012, Franz et al. 2013). Macedo et al. found conflicting results, when they studied 193 pregnant women and observed AIx to be significantly lower during pregnancy and changing with gestation, whereas PWV showed no change in gestation, and after adjustment for age and mean arterial pressure, there was no difference between the pregnant and the nonpregnant women (Macedo et al. 2008). However, arterial stiffness has also been postulated to increase with pregnancy. Wykretowicz et al. studied 46 women in the third trimester of pregnancy with a modified PWV and stated that they have slightly higher arterial stiffness in comparison with healthy nonpregnant, age- and height-matched controls. The authors speculated that the increased arterial stiffness might be secondary to the known physiological increase of cardiac output and the amount of circulating blood (Wykretowicz et al. 2011).

AASI is a relatively new index and therefore it has been studied during pregnancy in only one study apart from this present one. A recent study from Denmark had 59 pregnant women suffering from type I diabetes mellitus as subjects compared to 42 healthy pregnant controls (Lauszus et al. 2013). The diabetic subjects were studied in all three trimesters and

postpartum and the healthy ones during the 18th week of gestation and in the third trimester. In diabetic women, AASI was significantly higher at all times during pregnancy as compared to the postpartum situation (1st trimester 0.31 ± 0.16, 2nd 0.28 ± 0.16, 3rd 0.33 ± 0.18 vs. postpartum 0.22 ± 0.17; P <0.01) and AASI was directly associated with the albumin excretion rate. In normal pregnancies, an insignificant increase in AASI occurred from the 18th week (0.26 ± 0.19) to late pregnancy (0.32 ± 0.17). No difference was found in AASI between the diabetic women and non-diabetic controls during pregnancy.

The AASI values in the present study were in line with those in this Danish study. The normal value of AASI is proposed to be <0.50 at the age of 20 (Li et al. 2006b), and thus almost all of the values were within the normal range**.** The reason why no changes were detected in AASI during normal pregnancies might be that the women in the present study were young and healthy. On the other hand, in the study of Lauszus et al. the changes were seen because of the nature of diabetes mellitus type I, which is clearly associated with vasculopathy. In many cases, pregnancy can be even dangerous to diabetic women with reno-vascular comorbidity or retinopathy complications.

No association was found between a higher AASI and a lower birth weight, as one could have expected on the basis of a Dutch study. They studied 50 normotensive women and stated that PWV was associated with birth weight centile independently of blood pressure (Elvan-Taspinar et al. 2005). The inverse association between AASI and nocturnal dipping in the present studies was strong, which is in line with results in previous studies (Schillaci et al. 2007, Baumann et al. 2008, Ben-Dov et al. 2008). A positive correlation with age, an independent determinant of AASI (Li et al. 2006a), was found in the GDM study during pregnancy and in the normal pregnancy group after pregnancy, but not in hypertensive pregnancies. One may speculate that the pregnancy-specific changes in arterial elasticity overcame those related to maternal age. The negative correlation with height described as a determinant for AASI (Li et al. 2006a), was not detected in the Complicated Pregnancy Study. This could be due to the small variation in the maternal heights of the study subjects. Preeclampsia has been frequently associated with non-dipping. The results of this present study are in line with those of Brown et al. (Brown et al. 2001), who studied 186 hypertensive pregnant women and reported that nocturnal hypertension was more commonly present in preeclampsia than in gestational or essential hypertension (P <0.0001). In their study, sleep hypertensives had a significantly greater frequency of renal insufficiency. A significantly higher creatinine level in non-dippers was evident also in the present study. Nocturnal hypertension in preeclampsia could be associated with elevated levels of compounds involved in endothelial damage (Bouchlariotou et al. 2008). In the present study there was a clear and significant correlation between non-dipping and interleukin-6 levels.

The findings in study IV, the decrease in elasticity of the carotid artery during pregnancy, are in line with those of Mersich et al. who found a significant reduction in carotid compliance towards the end of pregnancy and then a recovery postpartum (Mersich et al. 2005). The values of a Chinese study also are in line with the present results (Yuan et al. 2013b). Yuan et al. studied 51 normal pregnant women during the third trimester. SI in the carotid artery was 35% higher in the pregnancy group as compared to value in the 30 women non-pregnant control group, whereas in the present study, the difference was even more marked, 47%. In addition, Yuan et al. measured the diameter of the carotid artery to be 13% larger than in non-pregnancy group; in the present study the value was 8%.

However, they examined some of the women twenty months after the delivery and all the parameters had returned to normal. Nevertheless, some similar studies report contrasting results. Hu et al. reported that in women with normal pregnancies SI remained unchanged but nonetheless the compliance increased (Hu et al. 2007). Spaanderman et al. demonstrated that arterial elasticity increased in carotid arteries as an accommodation for the increasing maternal cardiac output and elevated blood volume in early pregnancy (Spaanderman et al. 2000). However, in their study the last examination was conducted at 7 weeks of pregnancy and there was no follow-up data to determine what happened to carotid artery elasticity towards the end of the pregnancy.

6.3 VALIDITY AND LIMITATIONS OF THE STUDY

The Complicated Pregnancy Study examined a cohort of women with different pregnancy complications and a control group. It compared the vascular health in the different problem groups to the controls, and it was also possible to examine the same individuals again three months after the delivery. Study IV evaluated the pregnant cohort and matched controls from a large national prospective cohort study, the Cardiovascular Risk in Young Finns Study. The pregnant women were divided into three groups according to their gestational weeks, and there were no longitudinal data and no detailed information on their pregnancies or on the condition of the newborns.

Initially it was hoped to recruit 40-50 women per group for the Complicated Pregnancy Study. This was based on previous studies showing that in a sample of that size one could expect to detect an improvement in FMD (Corretti et al. 2002, De Roos et al. 2003). The patients with pregnancy complications were more challenging to enroll than expected, leaving far fewer study subjects than intended; the only group in which the desired size was achieved was the GDM. The study protocol in the Complicated Pregnancy Study was quite demanding spending one whole day in hospital after an all-night fasting, when ultrasound studies and head-up tilts were performed followed by 24-h ABPM. A study carried out on pregnant women recommended that a withdrawal rate of approximately 15% should be considered in ABPM studies in pregnant subjects (Walker et al. 2004), with sleep disturbance associated with the measurements being the major cause of noncompliance. Subjective sleep complaints are common during pregnancy due to the enlarging uterus, contractions and nocturia, and these are often even more pronounced in pregnancy complications (Ekholm et al. 1992, Nikkola et al. 1996). In addition to the demanding study protocol, one reason for the large number of drop-outs was obviously the newborn baby requiring all the mother's attention.

Another reason for statistically insignificant differences in the present study may have been the mildness of the complications in these study subjects. For instance, the disorders in the preeclampsia group were not very severe. This is because of the time of recruitment (about 34 ± 3 pregnancy weeks) and due to the fact that at that time those pregnancies complicated by the most severe preterm preeclampsia had already been treated by caesarean section or by induction of labor. Furthermore, the majority of GDM patients had a mild form of the disease; at the time of recruitment the normal OGTT values for pregnant women were lower than 4.8 - 11.2 - 9.9 mmol/l (fasting- 1h- 2h), but nowadays they are

below 5.3 – 10 – 8.6 mmol/l. The majority of the GDM group women (91,7%) had a fasting glucose value just over the old limit, implying that many of them would not be diagnosed as having GDM nowadays. However, the glucose level threshold at which the pregnancy risks increase is still unclear (HAPO Study Cooperative Research Group 2008). When this group was divided into diet/insulin subgroups, some significant differences did appear between pregnancy and postpartum, and for instance, it would be interesting to determine what happens to AASI in a larger sample of insulin-using GDM women.

In twin pregnancies, the chorionicity was not registered, nor was it checked if the pregnancy was due to artificial reproductive therapy.

No alternative method was used to assess arterial stiffness other than AASI. For example, a comparison with PWV as a "golden standard" would have provided more information about AASI's true usefulness during pregnancy.

In the Cardiovascular Risk in Young Finns Study no information was available on the potential preexisting disorders of the women or any possible complications in pregnancies such as gestational hypertension and GDM. This is of course a limitation but it seems most unlikely that those subjects with severe pregnancy complications would have been willing to participate in these rather demanding examinations. On the other hand, some preexisting disorders could also have been present in the control group. The Cardiovascular Risk in Young Finns Study, being a prospective cohort study, represents the total population. Another weakness of study IV is the lack of postpartum data. In this study, the method used to assess the carotid artery stiffness was valid and it was demonstrated that the changes seen during pregnancy were not due to an increase in the diameter of the artery.

In all the studies the sample sizes were small and a type II error is possible.

6.4 CLINICAL SIGNIFICANCE OF THE RESULTS

AASI is an index very easily obtained from the diurnal blood pressure values and it might be even available as additional information directly produced by the ABPM device. ABPM is becoming more common in the diagnostics of hypertension even during pregnancy. In order, to determine the validity and limitations of AASI information in pregnant women, it was important to explore its usefulness during different types of pregnancy. It is possible to conclude that the differences in AASI during pregnancy were not very convincing and the method cannot be recommended for use in diagnostics or predicting pregnancy complications. In severe preeclampsia or in pregnancies of DM type I women with pregravid vasculopathy, changes in AASI may be observed, but those situations are already known to be some of the pregnancies carrying the highest risks.

The result of study IV is interesting, but may not have clinical implications, since the decrease of carotid elasticity was probably a physiologic phenomenon. Despite the finding, of stiffening of the carotid artery, there is no evidence that the incidence of stroke would be elevated during pregnancy (Scott et al. 2012). Pregnant women are young and usually healthy with apparently healthy carotid arteries and therefore a stroke during normal pregnancy is a highly unlikely event in spite of the reduction in arterial elasticity.

6.5 GENERALIZABILITY OF THE RESULTS

If AASI really was affected by pregnancy itself, one would have expected to detect the change in Study I, in healthy pregnancies and certainly in twins in whom there are more pronounced cardiovascular changes. The changes in the pregnancy complications were minor and not linear, so it does seem that AASI is not sensitive enough to detect the changes in arterial stiffness occurring during pregnancy. The results would perhaps be different if conducted in subjects of races other than Caucasian or in studies with larger sample sizes. However, it is proposed that AASI is likely to be influenced by several factors such as heart rate, stroke volume and vasomotor tone as well as their circadian changes (Chirinos 2012); all of them being affected by pregnancy itself. This may be one reason why the present results are somewhat at odds with previous studies utilizing other methods, like PWV, with which to assess arterial stiffness during pregnancy. The changes seen in previous AASI studies were documented in older subjects with many more cardiovascular risk factors and diseases. Based on the present studies, it is not possible to recommend AASI for clinical use during pregnancy. Nevertheless, since AASI has been shown to be associated with risk of morbidity and mortality, if one does observe an abnormal AASI result outside the normal range in a pregnant individual, one should start to seek out possible risk factors and for example perhaps encourage lifestyle changes in this particular subject.

7 Conclusions

This study shows that ambulatory arterial stiffness index (AASI) is not sensitive enough to detect the changes in arterial stiffness occurring during third trimester of normal or mildly complicated pregnancy. No significant changes in AASI were found in normal singleton or twin pregnancies. The previously published correlations of AASI with nocturnal dipping and age were seen particularly three months postpartum, and thus one could speculate that the pregnancy-specific changes in arterial elasticity and hemodynamics overcame these effects during pregnancy. However, we did not use any other methods than AASI to show stiffness differences.

The only significant changes in AASI were seen in the GDM group. The women requiring insulin had higher postpartum AASI values than the GDM women on diet or the control group, i.e. some arterial stiffening occurred after the insulin therapy was terminated. In the GDM women controlled by diet there was a significant decrease in AASI three months after delivery, i.e. some recovery of elasticity, when the disturbance in glucose metabolism was normalized. However, the postpartum lipid, glucose and HOMA-IR values and BMIs were significantly higher in both GDM groups when compared to controls. Over the years following the index pregnancy, women with a history of GDM exhibit an enhanced cardiovascular risk profile and an increased incidence of type II diabetes and cardiovascular complications later in life.

In the hypertensive pregnancy disorders, no significant changes were detected in AASI values. In the preeclamptic women, a flattened dipping was seen and this was associated with increased IL-6, showing the systemic endothelial damage in this disease. However, these findings were not reflected in AASI results during pregnancy, though after pregnancy AASI seemed to be an early predictor of cardiovascular disease in conjunction with the dipping status. In addition, women with gestational hypertension or preeclampsia are known to have a many-fold elevated risk of developing later cardiovascular complications.

The present observations about the carotid artery stiffness during pregnancy revealed that the carotid artery elasticity declined towards the end of pregnancy but this was not correlated with the level of maternal hyperlipidemia or with changes in endothelial function in other parts of the maternal arterial tree. This phenomenon may actually be an appropriate adaptation to the hemodynamic changes occurring during pregnancy.

The importance of arterial stiffness as a risk factor for cardiovascular events has increased the enthusiasm to find methods to assess this parameter and to use it to identify those patients having an elevated cardiovascular risk. The earlier this can be done, the more benefit one can obtain from lifestyle intervention. Today, more and more women present with clusting of GDM, hypertension and obesity during pregnancy. At this sensitive time point, the subject may be more receptive to adopting a healthier lifestyle; these pregnant women should be thoroughly informed about the future cardiovascular risks, even although AASI does not seem to be a tool to pinpoint a specific risk. In pregnancies in DM type I women, changes in AASI might be observed, but it is already clear that the pregnancies in these women do carry a high risk.

References

Abalos, E., Cuesta, C., Grosso, A.L., Chou, D. & Say, L. 2013, "Global and regional estimates of preeclampsia and eclampsia: a systematic review", *European journal of obstetrics, gynecology, and reproductive biology,* vol. 170, no. 1, pp. 1-7.

Adiyaman, A., Dechering, D.G., Boggia, J., Li, Y., Hansen, T.W., Kikuya, M., Björklund-Bodegård, K., Richart, T., Thijs, L., Torp-Pedersen, C., Ohkubo, T., Dolan, E., Imai, Y., Sandoya, E., Ibsen, H., Wang, J., Lind, L., O'Brien, E., Thien, T., Staessen, J.A. & on behalf of the International Database on Ambulatory Blood Pressure Monitoring in Relation to Cardiovascular Outcomes Investigators 2008, "Determinants of the Ambulatory Arterial Stiffness Index in 7604 Subjects From 6 Populations", *Hypertension,* vol. 52, no: 6, pp. 1038-1044.

Anastasiou, E., Lekakis, J.P., Alevizaki, M., Papamichael, C.M., Megas, J., Souvatzoglou, A. & Stamatelopoulos, S.F. 1998, "Impaired endothelium-dependent vasodilatation in women with previous gestational diabetes", *Diabetes care,* vol. 21, no. 12, pp. 2111-2115.

Andersgaard, A.B., Acharya, G., Mathiesen, E.B., Johnsen, S.H., Straume, B. & Oian, P. 2012, "Recurrence and long-term maternal health risks of hypertensive disorders of pregnancy: a population-based study", *American Journal of Obstetrics and Gynecology,* vol. 206, no. 2, pp. 143.e1-143.e8.

Arioz, D.T., Saglam, H., Demirel, R., Koken, G., Cosar, E., Sahin, F.K., Dursun, H., Aral, I., Onrat, E. & Yilmazer, M. 2008, "Arterial stiffness and dipper/nondipper blood pressure status in women with preeclampsia", *Advances in Therapy,* vol. 25, no. 9, pp. 925-934.

Ayala, D.E., Hermida, R.C., Mojon, A., Fernandez, J.R. & Iglesias, M. 1997, "Circadian blood pressure variability in healthy and complicated pregnancies", *Hypertension,* vol. 30, no. 3 Pt 2, pp. 603-610.

Aznaouridis, K., Vlachopoulos, C., Protogerou, A. & Stefanadis, C. 2012, "Ambulatory systolic-diastolic pressure regression index as a predictor of clinical events: a meta-analysis of longitudinal studies", *Stroke; a journal of cerebral circulation,* vol. 43, no. 3, pp. 733-739.

Banerjee, M. & Cruickshank, J.K. 2006, "Pregnancy as the prodrome to vascular dysfunction and cardiovascular risk", *Nature clinical practice. Cardiovascular medicine,* vol. 3, no. 11, pp. 596-603.

Barden, A., Singh, R., Walters, B., Phillips, M. & Beilin, L.J. 2013, "A simple scoring method using cardiometabolic risk measurements in pregnancy to determine 10-year risk of type 2 diabetes in women with gestational diabetes", *Nutrition & diabetes,* vol. 3, pp. e72.

Bastos, J.M., Bertoquini, S. & Polonia, J. 2010, "Prognostic significance of ambulatory arterial stiffness index in hypertensives followed for 8.2 years: its relation with new events and cardiovascular risk estimation", *Revista portuguesa de cardiologia : orgao oficial da Sociedade Portuguesa de Cardiologia = Portuguese journal of cardiology : an official journal of the Portuguese Society of Cardiology,* vol. 29, no. 9, pp. 1287-1303.

Baumann, M., Dan, L., Nurnberger, J., Heemann, U. & Witzke, O. 2008, "Association of ambulatory arterial stiffness index and brachial pulse pressure is restricted to dippers", *Journal of hypertension,* vol. 26, no. 2, pp. 210-214.

Bellamy, L., Casas, J.P., Hingorani, A.D. & Williams, D.J. 2007, "Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis", *BMJ (Clinical research ed.),* vol. 335, no. 7627, pp. 974.

Ben-Dov, I., Gavish, B., Kark, J.D., Mekler, J. & Bursztyn, M. 2008, "A modified ambulatory arterial stiffness index is independently associated with all-cause mortality", *Journal of human hypertension,* vol. 22, no. 11, pp. 761-766.

Benetos, A., Adamopoulos, C., Bureau, J.M., Temmar, M., Labat, C., Bean, K., Thomas, F., Pannier, B., Asmar, R., Zureik, M., Safar, M. & Guize, L. 2002, "Determinants of accelerated progression of arterial stiffness in normotensive subjects and in treated hypertensive subjects over a 6-year period", *Circulation,* vol. 105, no. 10, pp. 1202-1207.

Berne, R.M. & Levy, M.N. 1996, "The Arterial System" in *Principles of physiology*, eds. R.M. Berne & M.N. Levy, 2.th edn, Kosby, St.Louis, pp. 289-300.

Berni, A., Ciani, E., Cecioni, I., Poggesi, L., Abbate, R. & Boddi, M. 2011, "Adherence to antihypertensive therapy affects Ambulatory Arterial Stiffness Index", *European journal of internal medicine,* vol. 22, no. 1, pp. 93-98.

Blacher, J., Guerin, A.P., Pannier, B., Marchais, S.J. & London, G.M. 2001, "Arterial calcifications, arterial stiffness, and cardiovascular risk in end-stage renal disease", *Hypertension,* vol. 38, no. 4, pp. 938-942.

Blacher, J., Guerin, A.P., Pannier, B., Marchais, S.J., Safar, M.E. & London, G.M. 1999, "Impact of aortic stiffness on survival in end-stage renal disease", *Circulation,* vol. 99, no. 18, pp. 2434-2439.

Bo, S., Valpreda, S., Menato, G., Bardelli, C., Botto, C., Gambino, R., Rabbia, C., Durazzo, M., Cassader, M., Massobrio, M. & Pagano, G. 2007, "Should we consider gestational diabetes a vascular risk factor?", *Atherosclerosis,* vol. 194, no. 2, pp. e72-9.

Bouchlariotou, S., Liakopoulos, V., Dovas, S., Giannopoulou, M., Kiropoulos, T., Zarogiannis, S., Gatselos, G., Zachopoulos, T., Kyriakou, D.S., Kallitsaris, A., Messinis, I. & Stefanidis, I. 2008, "Nocturnal hypertension is associated with an exacerbation of the endothelial damage in preeclampsia", *American Journal of Nephrology,* vol. 28, no. 3, pp. 424-430.

Breithaupt-Grogler, K., Ling, M., Boudoulas, H. & Belz, G.G. 1997, "Protective effect of chronic garlic intake on elastic properties of aorta in the elderly", *Circulation,* vol. 96, no. 8, pp. 2649-2655.

Brown, M. 2013, "Is there a role for ambulatory blood pressure monitoring in pregnancy?", *Clinical and experimental pharmacology & physiology,* May 8. doi: 10.1111/1440-1681.12106 .

Brown, M.A., Davis, G.K. & McHugh, L. 2001, "The prevalence and clinical significance of nocturnal hypertension in pregnancy", *Journal of hypertension,* vol. 19, no. 8, pp. 1437-1444.

Brown, M.A., Robinson, A., Bowyer, L., Buddle, M.L., Martin, A., Hargood, J.L. & Cario, G.M. 1998, "Ambulatory blood pressure monitoring in pregnancy: what is normal?", *American Journal of Obstetrics and Gynecology,* vol. 178, no. 4, pp. 836-842.

Bulzico, D.A., Zajdenverg, L., Cabizuca, C.A., de Oliveira, J.E. & Salles, G.F. 2012, "Assessment of arterial stiffness in women with gestational diabetes", *Diabetic medicine : a journal of the British Diabetic Association,* vol. 29, no. 2, pp. 227-231.

Cameron, J.D. & Cruickshank, J.K. 2007, "Glucose, insulin, diabetes and mechanisms of arterial dysfunction", *Clinical and experimental pharmacology & physiology,* vol. 34, no. 7, pp. 677-682.

Carpenter, M.W. 2007, "Gestational diabetes, pregnancy hypertension, and late vascular disease", *Diabetes care,* vol. 30 Suppl 2, pp. S246-50.

Chirinos, J.A. 2012, "Arterial stiffness: basic concepts and measurement techniques", *Journal of cardiovascular translational research,* vol. 5, no. 3, pp. 243-255.

Chobanian, A.V., Bakris, G.L., Black, H.R., Cushman, W.C., Green, L.A., Izzo, J.L.,Jr, Jones, D.W., Materson, B.J., Oparil, S., Wright, J.T.,Jr, Roccella, E.J., Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. National Heart, Lung, and Blood Institute & National High Blood Pressure Education Program Coordinating Committee 2003, "Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure", *Hypertension,* vol. 42, no. 6, pp. 1206-1252.

Chodick, G., Elchalal, U., Sella, T., Heymann, A.D., Porath, A., Kokia, E. & Shalev, V. 2010, "The risk of overt diabetes mellitus among women with gestational diabetes: a population-based study", *Diabetic medicine : a journal of the British Diabetic Association,* vol. 27, no. 7, pp. 779-785.

Corretti, M.C., Anderson, T.J., Benjamin, E.J., Celermajer, D., Charbonneau, F., Creager, M.A., Deanfield, J., Drexler, H., Gerhard-Herman, M., Herrington, D., Vallance, P., Vita, J., Vogel, R. & International Brachial Artery Reactivity Task Force 2002, "Guidelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilation of the brachial artery: a report of the International Brachial Artery Reactivity Task Force", *Journal of the American College of Cardiology,* vol. 39, no. 2, pp. 257-265.

Cuspidi, C., Macca, G., Sampieri, L., Fusi, V., Severgnini, B., Michev, I., Salerno, M., Magrini, F. & Zanchetti, A. 2001, "Target organ damage and non-dipping pattern defined by two sessions of ambulatory blood pressure monitoring in recently diagnosed essential hypertensive patients", *Journal of hypertension,* vol. 19, no. 9, pp. 1539-1545.

Davis, G.K., Mackenzie, C., Brown, M.A., Homer, C.S., Holt, J., McHugh, L. & Mangos, G. 2007, "Predicting transformation from gestational hypertension to preeclampsia in clinical practice: a possible role for 24 hour ambulatory blood pressure monitoring", *Hypertension in pregnancy : official journal of the International Society for the Study of Hypertension in Pregnancy,* vol. 26, no. 1, pp. 77-87.

De Roos, N.M., Bots, M.L., Schouten, E.G. & Katan, M.B. 2003, "Within-subject variability of flow-mediated vasodilation of the brachial artery in healthy men and women: implications for experimental studies", *Ultrasound in medicine & biology,* vol. 29, no. 3, pp. 401-406.

Dennis, A.T., Castro, J., Carr, C., Simmons, S., Permezel, M. & Royse, C. 2012, "Haemodynamics in women with untreated pre-eclampsia", *Anaesthesia,* vol. 67, no. 10, pp. 1105-1118.

Dolan, E., Thijs, L., Li, Y., Atkins, N., McCormack, P., McClory, S., O'Brien, E., Staessen, J.A. & Stanton, A.V. 2006a, "Ambulatory arterial stiffness index as a predictor of cardiovascular mortality in the Dublin Outcome Study", *Hypertension,* vol. 47, no. 3, pp. 365-370.

Dolan, E., Li, Y., Thijs, L., McCormack, P., Staessen, J.A., O'Brien, E. & Stanton, A. 2006b, "Ambulatory arterial stiffness index: rationale and methodology", *Blood pressure monitoring,* vol. 11, no. 2, pp. 103-105.

Edouard, D.A., Pannier, B.M., London, G.M., Cuche, J.L. & Safar, M.E. 1998, "Venous and arterial behavior during normal pregnancy", *The American Journal of Physiology,* vol. 274, no. 5 Pt 2, pp. H1605-12.

Ekholm, E.M., Polo, O., Rauhala, E.R. & Ekblad, U.U. 1992, "Sleep quality in preeclampsia", *American Journal of Obstetrics and Gynecology,* vol. 167, no. 5, pp. 1262-1266.

Elvan-Taspinar, A., Franx, A., Bots, M.L., Koomans, H.A. & Bruinse, H.W. 2005, "Arterial stiffness and fetal growth in normotensive pregnancy", *American journal of hypertension,* vol. 18, no. 3, pp. 337-341.

Estensen, M.E., Remme, E.W., Grindheim, G., Smiseth, O.A., Segers, P., Henriksen, T. & Aakhus, S. 2013, "Increased arterial stiffness in pre-eclamptic pregnancy at term and early and late postpartum: a combined echocardiographic and tonometric study", *American journal of hypertension,* vol. 26, no. 4, pp. 549-556.

Fagard, R.H., Celis, H., Thijs, L., Staessen, J.A., Clement, D.L., De Buyzere, M.L. & De Bacquer, D.A. 2008, "Daytime and nighttime blood pressure as predictors of death and cause-specific cardiovascular events in hypertension", *Hypertension,* vol. 51, no. 1, pp. 55-61.

Franz, M.B., Burgmann, M., Neubauer, A., Zeisler, H., Sanani, R., Gottsauner-Wolf, M., Schiessl, B. & Andreas, M. 2013, "Augmentation index and pulse wave velocity in normotensive and pre-eclamptic pregnancies", *Acta Obstetricia et Gynecologica Scandinavica,* .

Gaballa, M.A., Jacob, C.T., Raya, T.E., Liu, J., Simon, B. & Goldman, S. 1998, "Large artery remodeling during aging: biaxial passive and active stiffness", *Hypertension,* vol. 32, no. 3, pp. 437-443.

Garovic, V.D., Bailey, K.R., Boerwinkle, E., Hunt, S.C., Weder, A.B., Curb, D., Mosley, T.H.,Jr, Wiste, H.J. & Turner, S.T. 2010, "Hypertension in pregnancy as a risk factor for cardiovascular disease later in life", *Journal of hypertension,* vol. 28, no. 4, pp. 826-833.

Germain, A.M., Romanik, M.C., Guerra, I., Solari, S., Reyes, M.S., Johnson, R.J., Price, K., Karumanchi, S.A. & Valdes, G. 2007, "Endothelial dysfunction: a link among preeclampsia, recurrent pregnancy loss, and future cardiovascular events?", *Hypertension,* vol. 49, no. 1, pp. 90-95.

Giannarelli, C., Bianchini, E., Bruno, R.M., Magagna, A., Landini, L., Faita, F., Gemignani, V., Penno, G., Taddei, S. & Ghiadoni, L. 2012, "Local carotid stiffness and intima-media thickness assessment by a novel ultrasound-based system in essential hypertension", *Atherosclerosis,* vol. 223, no. 2, pp. 372-377.

Gomez-Marcos, M.A., Recio-Rodriguez, J.I., Patino-Alonso, M.C., Gomez-Sanchez, L., Agudo-Conde, C., Gomez-Sanchez, M., Rodriguez-Sanchez, E., Garcia-Ortiz, L. & Vasorisk group 2012, "Ambulatory arterial stiffness indices and target organ damage in hypertension", *BMC cardiovascular disorders,* vol. 12, pp. 1-2261-12-1.

Gosse, P., Papaioanou, G., Coulon, P., Reuter, S., Lemetayer, P. & Safar, M. 2007, "Can ambulatory blood-pressure monitoring provide reliable indices of arterial stiffness?", *American journal of hypertension,* vol. 20, no. 8, pp. 831-838.

Haluska, B.A., Jeffries, L., Carlier, S. & Marwick, T.H. 2010, "Measurement of arterial distensibility and compliance to assess prognosis", *Atherosclerosis,* vol. 209, no. 2, pp. 474-480.

Hamilton, P.K., Lockhart, C.J., Quinn, C.E. & McVeigh, G.E. 2007, "Arterial stiffness: clinical relevance, measurement and treatment", *Clinical science (London, England : 1979),* vol. 113, no. 4, pp. 157-170.

Hansen, T.W., Staessen, J.A., Torp-Pedersen, C., Rasmussen, S., Li, Y., Dolan, E., Thijs, L., Wang, J.G., O'Brien, E., Ibsen, H. & Jeppesen, J. 2006, "Ambulatory arterial stiffness index predicts stroke in a general population", *Journal of hypertension,* vol. 24, no. 11, pp. 2247-2253.

HAPO Study Cooperative Research Group; Metzger, B.E., Lowe, L.P., Dyer, A.R., Trimble, E.R., Chaovarindr, U., Coustan, D.R., Hadden, D.R., McCance, D.R., Hod, M., McIntyre, H.D., Oats, J.J., Persson, B., Rogers, M.S. & Sacks, D.A. 2008, "Hyperglycemia and adverse pregnancy outcomes", New England Journal of Medicine, vol. 358, no. 19, pp. 1991-2002.

Hashimoto, M., Miyamoto, Y., Iwai, C., Matsuda, Y., Hiraoka, E., Kanazawa, K., Nishimura, K., Sugiyama, D., Ito, K., Yamori, Y. & Akita, H. 2009, "Delivery may affect arterial elasticity in women", *Circulation journal : official journal of the Japanese Circulation Society,* vol. 73, no. 4, pp. 750-754.

Hausvater, A., Giannone, T., Sandoval, Y.H., Doonan, R.J., Antonopoulos, C.N., Matsoukis, I.L., Petridou, E.T. & Daskalopoulou, S.S. 2012, "The association between preeclampsia and arterial stiffness", *Journal of hypertension,* vol. 30, no. 1, pp. 17-33.

Hays, P.M., Cruikshank, D.P. & Dunn, L.J. 1985, "Plasma volume determination in normal and preeclamptic pregnancies", *American Journal of Obstetrics and Gynecology,* vol. 151, no. 7, pp. 958-966.

He, F.J., Marciniak, M., Visagie, E., Markandu, N.D., Anand, V., Dalton, R.N. & MacGregor, G.A. 2009, "Effect of modest salt reduction on blood pressure, urinary albumin, and pulse wave velocity in white, black, and Asian mild hypertensives", *Hypertension,* vol. 54, no. 3, pp. 482-488.

Heydari, M., Boutcher, Y.N. & Boutcher, S.H. 2013, "High-intensity intermittent exercise and cardiovascular and autonomic function", *Clinical autonomic research : official journal of the Clinical Autonomic Research Society,* vol. 23, no. 1, pp. 57-65.

Hirai, T., Sasayama, S., Kawasaki, T. & Yagi, S. 1989, "Stiffness of systemic arteries in patients with myocardial infarction. A noninvasive method to predict severity of coronary atherosclerosis", *Circulation,* vol. 80, no. 1, pp. 78-86.

Hu, J., Norman, M., Wallensteen, M. & Gennser, G. 1998, "Increased large arterial stiffness and impaired acetylcholine induced skin vasodilatation in women with previous gestational diabetes mellitus", *British journal of obstetrics and gynaecology,* vol. 105, no. 12, pp. 1279-1287.

Hu, S., Leonard, A., Seifalian, A. & Hardiman, P. 2007, "Vascular dysfunction during pregnancy in women with polycystic ovary syndrome", *Human reproduction (Oxford, England),* vol. 22, no. 6, pp. 1532-1539.

Hughes, A.D., Park, C., Davies, J., Francis, D., McG Thom, S.A., Mayet, J. & Parker, K.H. 2013, "Limitations of augmentation index in the assessment of wave reflection in normotensive healthy individuals", *PloS one,* vol. 8, no. 3, pp. e59371.

Ingelsson, E., Bjorklund-Bodegard, K., Lind, L., Arnlov, J. & Sundstrom, J. 2006, "Diurnal blood pressure pattern and risk of congestive heart failure", *JAMA : the journal of the American Medical Association,* vol. 295, no. 24, pp. 2859-2866.

James, P.R. & Nelson-Piercy, C. 2004, "Management of hypertension before, during, and after pregnancy", *Heart (British Cardiac Society),* vol. 90, no. 12, pp. 1499-1504.

Jerrard-Dunne, P., Mahmud, A. & Feely, J. 2008, "Ambulatory arterial stiffness index, pulse wave velocity and augmentation index--interchangeable or mutually exclusive measures?", *Journal of hypertension,* vol. 26, no. 3, pp. 529-534.

Juonala, M., Jarvisalo, M.J., Maki-Torkko, N., Kahonen, M., Viikari, J.S. & Raitakari, O.T. 2005, "Risk factors identified in childhood and decreased carotid artery elasticity in adulthood: the Cardiovascular Risk in Young Finns Study", *Circulation,* vol. 112, no. 10, pp. 1486-1493.

Juonala, M., Viikari, J.S., Laitinen, T., Marniemi, J., Helenius, H., Ronnemaa, T. & Raitakari, O.T. 2004, "Interrelations between brachial endothelial function and carotid intima-media thickness in young adults: the cardiovascular risk in young Finns study", *Circulation,* vol. 110, no. 18, pp. 2918-2923.

Kaihura, C., Savvidou, M.D., Anderson, J.M., McEniery, C.M. & Nicolaides, K.H. 2009, "Maternal arterial stiffness in pregnancies affected by preeclampsia", *American journal of physiology.Heart and circulatory physiology,* vol. 297, no. 2, pp. H759-64.

Kanbay, M., Turgut, F., Uyar, M.E., Akcay, A. & Covic, A. 2008, "Causes and mechanisms of nondipping hypertension", *Clinical and experimental hypertension (New York, N.Y.: 1993),* vol. 30, no. 7, pp. 585-597.

Kario, K., Matsuo, T., Kobayashi, H., Imiya, M., Matsuo, M. & Shimada, K. 1996, "Nocturnal fall of blood pressure and silent cerebrovascular damage in elderly hypertensive patients. Advanced silent cerebrovascular damage in extreme dippers", *Hypertension,* vol. 27, no. 1, pp. 130-135.

Kelly, R., Hayward, C., Avolio, A. & O'Rourke, M. 1989, "Noninvasive determination of age-related changes in the human arterial pulse", *Circulation,* vol. 80, no. 6, pp. 1652-1659.

Khalil, A., Jauniaux, E., Cooper, D. & Harrington, K. 2009, "Pulse wave analysis in normal pregnancy: a prospective longitudinal study", *PloS one,* vol. 4, no. 7, pp. e6134.

Khalil, A.A., Cooper, D.J. & Harrington, K.F. 2009b, "Pulse wave analysis: a preliminary study of a novel technique for the prediction of pre-eclampsia", *BJOG : an international journal of obstetrics and gynaecology,* vol. 116, no. 2, pp. 268-76; discussion 276-7.

Kikuya, M., Staessen, J.A., Ohkubo, T., Thijs, L., Metoki, H., Asayama, K., Obara, T., Inoue, R., Li, Y., Dolan, E., Hoshi, H., Hashimoto, J., Totsune, K., Satoh, H., Wang, J.G., O'Brien, E. & Imai, Y. 2007, "Ambulatory arterial stiffness index and 24-hour ambulatory pulse pressure as predictors of mortality in Ohasama, Japan", *Stroke; a journal of cerebral circulation,* vol. 38, no. 4, pp. 1161-1166.

Kim, C., Newton, K.M. & Knopp, R.H. 2002, "Gestational diabetes and the incidence of type 2 diabetes: a systematic review", *Diabetes care,* vol. 25, no. 10, pp. 1862-1868.

Kinlay, S., Creager, M.A., Fukumoto, M., Hikita, H., Fang, J.C., Selwyn, A.P. & Ganz, P. 2001, "Endothelium-derived nitric oxide regulates arterial elasticity in human arteries in vivo", *Hypertension,* vol. 38, no. 5, pp. 1049-1053.

Kohara, K., Nishida, W., Maguchi, M. & Hiwada, K. 1995, "Autonomic nervous function in non-dipper essential hypertensive subjects. Evaluation by power spectral analysis of heart rate variability", *Hypertension,* vol. 26, no. 5, pp. 808-814.

Kollias, A., Stergiou, G.S., Dolan, E. & O'Brien, E. 2012, "Ambulatory arterial stiffness index: a systematic review and meta-analysis", *Atherosclerosis,* vol. 224, no. 2, pp. 291-301.

Krause, T., Lovibond, K., Caulfield, M., McCormack, T., Williams, B. & Guideline Development Group 2011, "Management of hypertension: summary of NICE guidance", *BMJ (Clinical research ed.),* vol. 343, pp. d4891.

Laivuori, H., Tikkanen, M.J. & Ylikorkala, O. 1996, "Hyperinsulinemia 17 years after preeclamptic first pregnancy", *The Journal of clinical endocrinology and metabolism,* vol. 81, no. 8, pp. 2908-2911.

Laurent, S., Boutouyrie, P., Asmar, R., Gautier, I., Laloux, B., Guize, L., Ducimetiere, P. & Benetos, A. 2001, "Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients", *Hypertension,* vol. 37, no. 5, pp. 1236-1241.

Laurent, S., Cockcroft, J., Van Bortel, L., Boutouyrie, P., Giannattasio, C., Hayoz, D., Pannier, B., Vlachopoulos, C., Wilkinson, I., Struijker-Boudier, H. & European Network for Non-invasive Investigation of Large Arteries 2006, "Expert consensus document on arterial stiffness: methodological issues and clinical applications", *European heart journal,* vol. 27, no. 21, pp. 2588-2605.

Lauszus, F.F., Fuglsang, J., Rosgaard, A., Lousen, T. & Klebe, J.G. 2013, "Ambulatory arterial stiffness index in type 1 diabetes mellitus: any different during pregnancy?", *European journal of obstetrics, gynecology, and reproductive biology,* vol. 169, no: 2, pp. 234-238.

Lekakis, J.P., Zakopoulos, N.A., Protogerou, A.D., Papaioannou, T.G., Kotsis, V.T., Pitiriga, V.C., Tsitsirikos, M.D., Stamatelopoulos, K.S., Papamichael, C.M. & Mavrikakis, M.E. 2005, "Arterial stiffness assessed by pulse wave analysis in essential hypertension: relation to 24-h blood pressure profile", *International journal of cardiology,* vol. 102, no. 3, pp. 391-395.

Leoncini, G., Ratto, E., Viazzi, F., Vaccaro, V., Parodi, A., Falqui, V., Conti, N., Tomolillo, C., Deferrari, G. & Pontremoli, R. 2006, "Increased ambulatory arterial stiffness index is associated with target organ damage in primary hypertension", *Hypertension,* vol. 48, no. 3, pp. 397-403.

Li, Y., Dolan, E., Wang, J.G., Thijs, L., Zhu, D.L., Staessen, J.A., O'Brien, E. & Stanton, A. 2006a, "Ambulatory arterial stiffness index: determinants and outcome", *Blood pressure monitoring,* vol. 11, no. 2, pp. 107-110.

Li, Y., Wang, J.G., Dolan, E., Gao, P.J., Guo, H.F., Nawrot, T., Stanton, A.V., Zhu, D.L., O'Brien, E. & Staessen, J.A. 2006b, "Ambulatory arterial stiffness index derived from 24-hour ambulatory blood pressure monitoring", *Hypertension,* vol. 47, no. 3, pp. 359-364.

Li, Y., Dolan, E., Wang, J., Thijs, L., Zhu, D., Staessen, J.A., O'Brien, E. & Stanton, A. 2006c, "Ambulatory arterial stiffness index: determinants and outcome", *Blood pressure monitoring,* vol. 11, no. 2, pp. 107-110.

Littler, W.A. 1979, "Sleep and blood pressure: further observations", *American Heart Journal,* vol. 97, no. 1, pp. 35-37.

Lorenz, M.W., Markus, H.S., Bots, M.L., Rosvall, M. & Sitzer, M. 2007, "Prediction of clinical cardiovascular events with carotid intima-media thickness: a systematic review and meta-analysis", *Circulation,* vol. 115, no. 4, pp. 459-467.

Ma, X.J., Duan, Y.Y., Yuan, L.J., Cao, T.S., Wang, Y., Yang, H.G. & Chen, S. 2012, "Quantitative assessment of maternal common carotid artery mechanics using velocity vector imaging in pre-eclampsia", *European journal of obstetrics, gynecology, and reproductive biology,* vol. 160, no. 1, pp. 30-34.

Macedo, M.L., Luminoso, D., Savvidou, M.D., McEniery, C.M. & Nicolaides, K.H. 2008, "Maternal wave reflections and arterial stiffness in normal pregnancy as assessed by applanation tonometry", *Hypertension,* vol. 51, no. 4, pp. 1047-1051.

Macwilliam, J.A. & Melvin, G.S. 1914, "Systolic and Diastolic Blood Pressure Estimation, with Special Reference to the Auditory Method", *British medical journal,* vol. 1, no. 2778, pp. 693-697.

Mahendru, A.A., Everett, T.R., Wilkinson, I.B., Lees, C.C. & McEniery, C.M. 2012, "Maternal cardiovascular changes from pre-pregnancy to very early pregnancy", *Journal of hypertension,* vol. 30, no. 11, pp. 2168-2172.

Mahmud, A. & Feely, J. 2003, "Effect of smoking on arterial stiffness and pulse pressure amplification", *Hypertension,* vol. 41, no. 1, pp. 183-187.

Makkonen, N., Heinonen, S., Hongisto, T., Penttila, I. & Kirkinen, P. 2002, "Normalization of vasoactive changes in preeclampsia precedes clinical recovery", *Hypertension in pregnancy : official journal of the International Society for the Study of Hypertension in Pregnancy,* vol. 21, no. 1, pp. 51-64.

Mancia, G., Ferrari, A., Gregorini, L., Parati, G., Pomidossi, G., Bertinieri, G., Grassi, G., di Rienzo, M., Pedotti, A. & Zanchetti, A. 1983, "Blood pressure and heart rate variabilities in normotensive and hypertensive human beings", *Circulation research,* vol. 53, no. 1, pp. 96-104.

Mannisto, T., Mendola, P., Vaarasmaki, M., Jarvelin, M.R., Hartikainen, A.L., Pouta, A. & Suvanto, E. 2013, "Elevated blood pressure in pregnancy and subsequent chronic disease risk", *Circulation,* vol. 127, no. 6, pp. 681-690.

Marlatt, K.L., Kelly, A.S., Steinberger, J. & Dengel, D.R. 2012, "The influence of gender on carotid artery compliance and distensibility in children and adults", *Journal of clinical ultrasound : JCU,* .

Matthews, D.R., Hosker, J.P., Rudenski, A.S., Naylor, B.A., Treacher, D.F. & Turner, R.C. 1985, "Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man", *Diabetologia,* vol. 28, no. 7, pp. 412-419.

McEniery, C.M., Spratt, M., Munnery, M., Yarnell, J., Lowe, G.D., Rumley, A., Gallacher, J., Ben-Shlomo, Y., Cockcroft, J.R. & Wilkinson, I.B. 2010, "An analysis of prospective risk factors for aortic stiffness in men: 20-year follow-up from the Caerphilly prospective study", *Hypertension,* vol. 56, no. 1, pp. 36-43.

McEniery, C.M., Wallace, S., Mackenzie, I.S., McDonnell, B., Yasmin, Newby, D.E., Cockcroft, J.R. & Wilkinson, I.B. 2006, "Endothelial function is associated with pulse pressure, pulse wave velocity, and augmentation index in healthy humans", *Hypertension,* vol. 48, no. 4, pp. 602-608.

Mersich, B., Rigo, J.,Jr, Besenyei, C., Lenard, Z., Studinger, P. & Kollai, M. 2005, "Opposite changes in carotid versus aortic stiffness during healthy human pregnancy", *Clinical science (London, England : 1979),* vol. 109, no. 1, pp. 103-107.

Mitchell, G.F. 2004, "Arterial stiffness and wave reflection in hypertension: pathophysiologic and therapeutic implications", *Current hypertension reports,* vol. 6, no. 6, pp. 436-441.

Mule, G., Cottone, S., Cusimano, P., Incalcaterra, F., Giandalia, M., Costanzo, M., Nardi, E., Palermo, A., Geraci, C., Costa, R. & Cerasola, G. 2008, "Inverse relationship between ambulatory arterial stiffness index and glomerular filtration rate in arterial hypertension", *American journal of hypertension,* vol. 21, no. 1, pp. 35-40.

Muxfeldt, E.S., Cardoso, C.R., Dias, V.B., Nascimento, A.C. & Salles, G.F. 2010, "Prognostic impact of the ambulatory arterial stiffness index in resistant hypertension", *Journal of hypertension,* vol. 28, no. 7, pp. 1547-1553.

Myung, Y., Seo, H.S., Jung, I.H., Lee, N.H., Suh, J., Choi, J.H. & Cho, Y.H. 2012, "The correlation of carotid artery stiffness with heart function in hypertensive patients", *Journal of cardiovascular ultrasound,* vol. 20, no. 3, pp. 134-139.

Nikkola, E., Ekblad, U., Ekholm, E., Mikola, H. & Polo, O. 1996, "Sleep in multiple pregnancy: breathing patterns, oxygenation, and periodic leg movements", *American Journal of Obstetrics and Gynecology,* vol. 174, no. 5, pp. 1622-1625.

Nurnberger, J., Keflioglu-Scheiber, A., Opazo Saez, A.M., Wenzel, R.R., Philipp, T. & Schafers, R.F. 2002, "Augmentation index is associated with cardiovascular risk", *Journal of hypertension,* vol. 20, no. 12, pp. 2407-2414.

O'Brien, E., Asmar, R., Beilin, L., Imai, Y., Mancia, G., Mengden, T., Myers, M., Padfield, P., Palatini, P., Parati, G., Pickering, T., Redon, J., Staessen, J., Stergiou, G., Verdecchia, P. & European Society of Hypertension Working Group on Blood Pressure Monitoring 2005, "Practice guidelines of the European Society of Hypertension for clinic, ambulatory and self blood pressure measurement", *Journal of hypertension,* vol. 23, no. 4, pp. 697-701.

O'Brien, E., Sheridan, J. & O'Malley, K. 1988, "Dippers and non-dippers", *Lancet,* vol. 2, no. 8607, pp. 397.

Ohkubo, T., Imai, Y., Tsuji, I., Nagai, K., Watanabe, N., Minami, N., Kato, J., Kikuchi, N., Nishiyama, A., Aihara, A., Sekino, M., Satoh, H. & Hisamichi, S. 1997, "Relation between nocturnal decline in blood pressure and mortality. The Ohasama Study", *American journal of hypertension,* vol. 10, no. 11, pp. 1201-1207.

O'Rourke, M.F., Staessen, J.A., Vlachopoulos, C., Duprez, D. & Plante, G.E. 2002a, "Clinical applications of arterial stiffness; definitions and reference values", *American journal of hypertension,* vol. 15, no. 5, pp. 426-444.

O'Rourke, M.F., Staessen, J.A., Vlachopoulos, C., Duprez, D. & Plante, G.E. 2002b, "Clinical applications of arterial stiffness; definitions and reference values", *American journal of hypertension,* vol. 15, no. 5, pp. 426-444.

Paik, J.K., Kim, M., Kwak, J.H., Lee, E.K., Lee, S. & Lee, J.H. "Increased arterial stiffness in subjects with impaired fasting glucose", *Journal of diabetes and its complications,* , no. 0.

Palmas, W., Pickering, T., Eimicke, J.P., Moran, A., Teresi, J., Schwartz, J.E., Field, L., Weinstock, R.S. & Shea, S. 2007, "Value of ambulatory arterial stiffness index and 24-h pulse pressure to predict progression of albuminuria in elderly people with diabetes mellitus", *American journal of hypertension,* vol. 20, no. 5, pp. 493-500.

Paradisi, G., Biaggi, A., Ferrazzani, S., De Carolis, S. & Caruso, A. 2002, "Abnormal carbohydrate metabolism during pregnancy : association with endothelial dysfunction", *Diabetes care,* vol. 25, no. 3, pp. 560-564.

Parati, G., Pomidossi, G., Casadei, R., Malaspina, D., Colombo, A., Ravogli, A. & Mancia, G. 1985, "Ambulatory blood pressure monitoring does not interfere with the haemodynamic effects of sleep", *Journal of hypertension.Supplement : official journal of the International Society of Hypertension,* vol. 3, no. 2, pp. S107-9.

Parati, G. & Schillaci, G. 2012, "What are the real determinants of the ambulatory arterial stiffness index?", *Journal of hypertension,* vol. 30, no. 3, pp. 472-476.

Phillips, J.K., Janowiak, M., Badger, G.J. & Bernstein, I.M. 2010, "Evidence for distinct preterm and term phenotypes of preeclampsia", *The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians,* vol. 23, no. 7, pp. 622-626.

Pitsavos, C., Toutouzas, K., Dernellis, J., Skoumas, J., Skoumbourdis, E., Stefanadis, C. & Toutouzas, P. 1998, "Aortic stiffness in young patients with heterozygous familial hypercholesterolemia", *American Heart Journal,* vol. 135, no. 4, pp. 604-608.

Poppas, A., Shroff, S.G., Korcarz, C.E., Hibbard, J.U., Berger, D.S., Lindheimer, M.D. & Lang, R.M. 1997, "Serial assessment of the cardiovascular system in normal pregnancy. Role of arterial compliance and pulsatile arterial load", *Circulation,* vol. 95, no. 10, pp. 2407-2415.

Powe, C.E., Levine, R.J. & Karumanchi, S.A. 2011, "Preeclampsia, a disease of the maternal endothelium: the role of antiangiogenic factors and implications for later cardiovascular disease", *Circulation,* vol. 123, no. 24, pp. 2856-2869.

Raitakari, O.T., Juonala, M., Kahonen, M., Taittonen, L., Laitinen, T., Maki-Torkko, N., Jarvisalo, M.J., Uhari, M., Jokinen, E., Ronnemaa, T., Akerblom, H.K. & Viikari, J.S. 2003, "Cardiovascular risk factors in childhood and carotid artery intima-media thickness in adulthood: the Cardiovascular Risk in Young Finns Study", *JAMA : the journal of the American Medical Association,* vol. 290, no. 17, pp. 2277-2283.

Reference Values for Arterial Stiffness' Collaboration 2010, "Determinants of pulse wave velocity in healthy people and in the presence of cardiovascular risk factors: 'establishing normal and reference values'", *European heart journal,* vol. 31, no. 19, pp. 2338-2350.

Retnakaran, R. 2009, "Glucose tolerance status in pregnancy: a window to the future risk of diabetes and cardiovascular disease in young women", *Current diabetes reviews,* vol. 5, no. 4, pp. 239-244.

Riley, W.A., Barnes, R.W., Evans, G.W. & Burke, G.L. 1992, "Ultrasonic measurement of the elastic modulus of the common carotid artery. The Atherosclerosis Risk in Communities (ARIC) Study", *Stroke; a journal of cerebral circulation,* vol. 23, no. 7, pp. 952-956.

Robb, A.O., Mills, N.L., Din, J.N., Smith, I.B., Paterson, F., Newby, D.E. & Denison, F.C. 2009, "Influence of the menstrual cycle, pregnancy, and preeclampsia on arterial stiffness", *Hypertension,* vol. 53, no. 6, pp. 952-958.

Rogers, D.T., Colon, M., Gambala, C., Wilkins, I. & Hibbard, J.U. 2010, "Effects of magnesium on central arterial compliance in preeclampsia", *American Journal of Obstetrics and Gynecology,* vol. 202, no. 5, pp. 448.e1-448.e8.

Romundstad, P.R., Magnussen, E.B., Smith, G.D. & Vatten, L.J. 2010, "Hypertension in pregnancy and later cardiovascular risk: common antecedents?", *Circulation,* vol. 122, no. 6, pp. 579-584.

Ronnback, M., Lampinen, K., Groop, P.H. & Kaaja, R. 2005, "Pulse wave reflection in currently and previously preeclamptic women", *Hypertension in pregnancy : official journal of the International Society for the Study of Hypertension in Pregnancy,* vol. 24, no. 2, pp. 171-180.

Ross, J.J. & Schmid-Schoenbein, G. 1991, "Dynamics of the peripheral circulation" in *Best and Taylor's physiological basis of medical practice*, ed. J.B. West, 12.th edn, Williams & Wilkins, Baltimore, pp. 138-158.

Routledge, F.S., McFetridge-Durdle, J.A., Dean, C.R. & Canadian Hypertension Society 2007, "Night-time blood pressure patterns and target organ damage: a review", *The Canadian journal of cardiology,* vol. 23, no. 2, pp. 132-138.

Saarelainen, H., Karkkainen, H., Valtonen, P., Punnonen, K., Laitinen, T., Heiskanen, N., Lyyra-Laitinen, T., Vanninen, E. & Heinonen, S. 2012, "Flow-mediated vasodilation is not attenuated in hypertensive pregnancies despite biochemical signs of inflammation", *ISRN obstetrics and gynecology,* vol. 2012, pp. 709464.

Saarelainen, H., Laitinen, T., Raitakari, O.T., Juonala, M., Heiskanen, N., Lyyra-Laitinen, T., Viikari, J.S., Vanninen, E. & Heinonen, S. 2006, "Pregnancy-related hyperlipidemia and endothelial function in healthy women", *Circulation journal : official journal of the Japanese Circulation Society,* vol. 70, no. 6, pp. 768-772.

Safar, M.E. 1996, "Carotid artery stiffness with applications to cardiovascular pharmacology", *General pharmacology,* vol. 27, no. 8, pp. 1293-1302.

Sagawa, K., Lie, R.K. & Schaefer, J. 1990, "Translation of Otto Frank's paper "Die Grundform des Arteriellen Pulses" Zeitschrift fur Biologie 37: 483-526 (1899)", *Journal of Molecular and Cellular Cardiology,* vol. 22, no. 3, pp. 253-254.

Savvidou, M.D., Anderson, J.M., Kaihura, C. & Nicolaides, K.H. 2010, "Maternal arterial stiffness in pregnancies complicated by gestational and type 2 diabetes mellitus", *American Journal of Obstetrics and Gynecology,* vol. 203, no. 3, pp. 274.e1-274.e7.

Savvidou, M.D., Kaihura, C., Anderson, J.M. & Nicolaides, K.H. 2011, "Maternal arterial stiffness in women who subsequently develop pre-eclampsia", *PloS one,* vol. 6, no. 5, pp. e18703.

Schillaci, G., Parati, G., Pirro, M., Pucci, G., Mannarino, M.R., Sperandini, L. & Mannarino, E. 2007, "Ambulatory arterial stiffness index is not a specific marker of reduced arterial compliance", *Hypertension,* vol. 49, no. 5, pp. 986-991.

Scott, C.A., Bewley, S., Rudd, A., Spark, P., Kurinczuk, J.J., Brocklehurst, P. & Knight, M. 2012, "Incidence, risk factors, management, and outcomes of stroke in pregnancy", *Obstetrics and gynecology,* vol. 120, no. 2 Pt 1, pp. 318-324.

Sherwood, A., Steffen, P.R., Blumenthal, J.A., Kuhn, C. & Hinderliter, A.L. 2002, "Nighttime blood pressure dipping: the role of the sympathetic nervous system", *American journal of hypertension,* vol. 15, no. 2 Pt 1, pp. 111-118.

Simons, P.C.G., Algra, A., Bots, M.L., Grobbee, D.E., van der Graaf, Y. & for the SMART Study Group 1999, "Common Carotid Intima-Media Thickness and Arterial Stiffness: Indicators of Cardiovascular Risk in High-Risk Patients The SMART Study (Second Manifestations of ARTerial disease)", *Circulation,* vol. 100, no. 9, pp. 951-957.

Sipilä, K., Koivistoinen, T., Moilanen, L., Nieminen, T., Reunanen, A., Jula, A., Salomaa, V., Kaaja, R., Kööbi, T., Kukkonen-Harjula, K., Majahalme, S. & Kähönen, M. 2007, "Metabolic syndrome and arterial stiffness: The Health 2000 Survey", *Metabolism,* vol. 56, no. 3, pp. 320-326.

Sobiczewski, W., Wirtwein, M. & Gruchala, M. 2013, "Ambulatory systolic-diastolic pressure regression index predicts acute coronary syndromes", *Blood pressure,* vol. 22, no. 3, pp. 179-182.

Spaanderman, M.E., Willekes, C., Hoeks, A.P., Ekhart, T.H. & Peeters, L.L. 2000, "The effect of pregnancy on the compliance of large arteries and veins in healthy parous control subjects and women with a history of preeclampsia", *American Journal of Obstetrics and Gynecology,* vol. 183, no. 5, pp. 1278-1286.

Staessen, J.A., Bieniaszewski, L., O'Brien, E., Gosse, P., Hayashi, H., Imai, Y., Kawasaki, T., Otsuka, K., Palatini, P., Thijs, L., Fagard, R. & on behalf of the 'Ad Hoc' Working Group 1997, "Nocturnal Blood Pressure Fall on Ambulatory Monitoring in a Large International Database", *Hypertension,* vol. 29, no. 1, pp. 30-39.

Steegers, E.A., von Dadelszen, P., Duvekot, J.J. & Pijnenborg, R. 2010, "Pre-eclampsia", *The Lancet,* vol. 376, no. 9741, pp. 631-644.

Sullivan, S.D., Umans, J.G. & Ratner, R. 2012, "Gestational diabetes: implications for cardiovascular health", *Current diabetes reports,* vol. 12, no. 1, pp. 43-52.

Tanaka, M., Sugawara, M., Ogasawara, Y., Izumi, T., Niki, K. & Kajiya, F. 2013, "Intermittent, moderate-intensity aerobic exercise for only eight weeks reduces arterial stiffness: evaluation by measurement of stiffness parameter and pressure-strain elastic modulus by use of ultrasonic echo tracking", *Journal of medical ultrasonics (2001),* vol. 40, no. 2, pp. 119-124.

THL 2012, *National Institute for Health and Welfare. Deliveries and birth 2010. Statistical report 27/2011, Finland (THL), 2012.* . Available: http://urn.fi/URN:NBN:fi-fe201301171623.

Thorne, S.A. 2004, "Pregnancy in heart disease", *Heart (British Cardiac Society),* vol. 90, no. 4, pp. 450-456.

Tihtonen, K.M., Koobi, T. & Uotila, J.T. 2006, "Arterial stiffness in preeclamptic and chronic hypertensive pregnancies", *European journal of obstetrics, gynecology, and reproductive biology,* vol. 128, no. 1-2, pp. 180-186.

Tomlinson, L.A. 2012, "Methods for assessing arterial stiffness: technical considerations", *Current opinion in nephrology and hypertension,* vol. 21, no. 6, pp. 655-660.

Tsioufis, C., Antoniadis, D., Stefanadis, C., Tzioumis, K., Pitsavos, C., Kallikazaros, I., Psarros, T., Lalos, S., Michaelides, A. & Toutouzas, P. 2002, "Relationships between new risk factors and circadian blood pressure variation in untreated subjects with essential hypertension", *American journal of hypertension,* vol. 15, no. 7 Pt 1, pp. 600-604.

Uebing, A., Steer, P.J., Yentis, S.M. & Gatzoulis, M.A. 2006, "Pregnancy and congenital heart disease", *BMJ (Clinical research ed.),* vol. 332, no. 7538, pp. 401-406.

Ulusoy, R.E., Demiralp, E., Kirilmaz, A., Kilicaslan, F., Ozmen, N., Kucukarslan, N., Kardesoglu, E., Tutuncu, L., Keskin, O. & Cebeci, B.S. 2006, "Aortic elastic properties in young pregnant women", *Heart and vessels,* vol. 21, no. 1, pp. 38-41.

Urbina, E.M., Srinivasan, S.R., Kieltyka, R.L., Tang, R., Bond, M.G., Chen, W. & Berenson, G.S. 2004, "Correlates of carotid artery stiffness in young adults: The Bogalusa Heart Study", *Atherosclerosis,* vol. 176, no. 1, pp. 157-164.

Valensise, H., Vasapollo, B., Gagliardi, G. & Novelli, G.P. 2008, "Early and late preeclampsia: two different maternal hemodynamic states in the latent phase of the disease", *Hypertension,* vol. 52, no. 5, pp. 873-880.

Vatten, L.J. & Skjaerven, R. 2004, "Is pre-eclampsia more than one disease?", *BJOG : an international journal of obstetrics and gynaecology,* vol. 111, no. 4, pp. 298-302.

Verdecchia, P., Schillaci, G., Gatteschi, C., Zampi, I., Battistelli, M., Bartoccini, C. & Porcellati, C. 1993, "Blunted nocturnal fall in blood pressure in hypertensive women with future cardiovascular morbid events", *Circulation,* vol. 88, no. 3, pp. 986-992.

Verdecchia, P. 2000, "Prognostic Value of Ambulatory Blood Pressure: Current Evidence and Clinical Implications", *Hypertension,* vol. 35, no. 3, pp. 844-851.

Visontai, Z., Lenard, Z., Studinger, P., Rigo, J.,Jr & Kollai, M. 2002, "Impaired baroreflex function during pregnancy is associated with stiffening of the carotid artery", *Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology,* vol. 20, no. 4, pp. 364-369.

Vlachopoulos, C., Aznaouridis, K., O'Rourke, M.F., Safar, M.E., Baou, K. & Stefanadis, C. 2010a, "Prediction of cardiovascular events and all-cause mortality with central haemodynamics: a systematic review and meta-analysis", *European heart journal,* vol. 31, no. 15, pp. 1865-1871.

Vlachopoulos, C., Aznaouridis, K. & Stefanadis, C. 2010b, "Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis", *Journal of the American College of Cardiology,* vol. 55, no. 13, pp. 1318-1327.

Walker, S.P., Permezel, M.J., Brennecke, S.P., Tuttle, L.K. & Higgins, J.R. 2004, "Patient satisfaction with the SpaceLabs 90207 ambulatory blood pressure monitor in pregnancy", *Hypertension in pregnancy : official journal of the International Society for the Study of Hypertension in Pregnancy,* vol. 23, no. 3, pp. 295-301.

Wang, M.C., Tsai, W.C., Chen, J.Y. & Huang, J.J. 2005, "Stepwise increase in arterial stiffness corresponding with the stages of chronic kidney disease", *American Journal of Kidney Diseases : The Official Journal of the National Kidney Foundation,* vol. 45, no. 3, pp. 494-501.

Wang, X., Keith, J.C.,Jr, Struthers, A.D. & Feuerstein, G.Z. 2008, "Assessment of arterial stiffness, a translational medicine biomarker system for evaluation of vascular risk", *Cardiovascular therapeutics,* vol. 26, no. 3, pp. 214-223.

Watanabe, N., Imai, Y., Nagai, K., Tsuji, I., Satoh, H., Sakuma, M., Sakuma, H., Kato, J., Onodera-Kikuchi, N., Yamada, M., Abe, F., Hisamichi, S. & Abe, K. 1996, "Nocturnal blood pressure and silent cerebrovascular lesions in elderly Japanese", *Stroke; a journal of cerebral circulation,* vol. 27, no. 8, pp. 1319-1327.

Wilkinson, I.B., MacCallum, H., Hupperetz, P.C., van Thoor, C.J., Cockcroft, J.R. & Webb, D.J. 2001, "Changes in the derived central pressure waveform and pulse pressure in response to angiotensin II and noradrenaline in man", *The Journal of Physiology,* vol. 530, no. 3, pp. 541-550.

Working group set up by the Finnish Medical Society Duodecim and the Finnish Hypertension Society 2009, *Hypertension (online). Current Care Guideline.http://www.kaypahoito.fi] webcite* [Homepage of Finnish Medical Society Duodecim], [Online].

Wykretowicz, M., Krauze, T., Guzik, P., Piskorski, J., Markwitz, W., Wykretowicz, A. & Wysocki, H. 2011, "Arterial stiffness, central hemodynamics and wave reflection in normal pregnancy and control nonpregnant women", *European journal of obstetrics, gynecology, and reproductive biology,* vol. 159, no. 1, pp. 49-52.

Yuan, L.J., Xue, D., Duan, Y.Y., Cao, T.S., Yang, H.G. & Zhou, N. 2013a, "Carotid intima-media thickness and arterial stiffness in preeclampsia by analysis with a radio-frequency ultrasound technique", *Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology,* .

Yuan, L.J., Xue, D., Duan, Y.Y., Cao, T.S. & Zhou, N. 2013b, "Maternal carotid remodeling and increased carotid arterial stiffness in normal late-gestational pregnancy as assessed by radio-frequency ultrasound technique", *BMC pregnancy and childbirth,* vol. 13, no. 1, pp. 122.

Zebekakis, P.E., Nawrot, T., Thijs, L., Balkestein, E.J., van der Heijden-Spek, J., Van Bortel, L.M., Struijker-Boudier, H.A., Safar, M.E. & Staessen, J.A. 2005, "Obesity is associated with increased arterial stiffness from adolescence until old age", *Journal of hypertension,* vol. 23, no. 10, pp. 1839-1846.

Zhang, P., Guo, R., Xiao, D., Chu, S., Gong, L., Zhang, C., Jing, B. & Li, M. 2012, "Influence of smoking cessation on carotid artery wall elasticity evaluated by echo-tracking", *Journal of clinical ultrasound : JCU,* vol. 40, no. 6, pp. 352-356.

Åkerblom, H.K., Viikari, J., Uhari, M., Räsänen, L., Byckling, T., Louhivuori, K., Pesonen, E., Suoninen, P., Pietikäinen, M., Lähde, P.L., Dahl, M., Aromaa, A., Sarna, S., and Pyörälä, K. 1985, ”Atherosclerosis precursors in Finnish children and adolescents. I. General description of the cross-sectional study of 1980, and an account of the children’s and families’ state of health”, *Acta paediatrica Scandinavica*, vol. 74, no. s318, pp. 49-63.

Henna Kärkkäinen

The Ambulatory Arterial Stiffness Index and Carotid Stiffness in Pregnancy

The importance of arterial stiffness as a risk factor for cardiovascular events has resulted in much research attempting to devise a method to assess this parameter and subsequently to identify patients with greater than normal cardiovascular risks. The objective of this study was to assess arterial stiffness in normal and complicated pregnancies and three months postpartum. The method used was ambulatory arterial stiffness index (AASI), which is based on an individual's 24-hour ambulatory blood pressure measurement.

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