Maternal cardiac function, uterine artery hemodynamics and natriuretic peptides at 22-24 weeks of gestation and subsequent development of hypertensive disorders of pregnancy

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Abstract

Introduction: Maternal cardiac dysfunction as well as abnormal uterine artery (UtA) Doppler are associated with hypertensive disorders of pregnancy (HDP), but their relationship is unclear. We investigated the correlation between maternal cardiac function, UtA hemodynamics and natriuretic peptides; and explored differences between women who subsequently develop HDP and those who did not.

Material and methods: This was a prospective cross-sectional cohort study of 347 pregnant women at 22-24 weeks. Maternal cardiac function and systemic hemodynamics was investigated at baseline and after 90 seconds of passive leg raising (PLR) using impedance cardiography. Preload reserve was defined as percent change (Δ%) in stroke volume (SV) and cardiac output (CO) from baseline to PLR. UtA hemodynamics was studied using Doppler ultrasonography. UtA blood flow, resistance and pulsatility index (PI) were calculated. Fasting venous blood samples were analyzed for natriuretic peptides (proANP, Nt-proBNP and CNP). The course and outcome of pregnancy was recorded.

Results: At baseline, ProANP correlated significantly with CO (r= -0.122; p=0.023) and left cardiac work index (r= -0.112; p=0.037), whereas Nt-ProBNP correlated significantly with acceleration index (r=0.127; p=0.018) and velocity index (r= -0.111; p=0.039. CNP correlated significantly with UtA blood flow (r=0.118; p=0.028) and resistance (r= -0.112; p=0.037) but not with UtA PI (r=0.034; p=0.523). None of the natriuretic peptides correlated with preload reserve.

At 22-24 weeks, women who subsequently developed HDP had lower UtA blood flow (552 vs. 692 ml/min; p=0.028), higher UtA resistance (0.28 vs. 0.17mmHg/mL/min; p=0.004) and higher mean UtA PI (1.12 vs. 0.84; p<0.001) compared to those who did not, but had similar natriuretic peptide levels. Women developing HDP had significantly higher increase in SV and CO and more reduction in systemic vascular resistance following PLR compared with the reference group. Left cardiac work index, acceleration index, and velocity index decreased following PLR in the reference group, whereas they increased in women who later developed HDP.

Conclusions: ProANP correlated with CO and cardiac work, Nt-proBNP with indices of cardiac contractility, and CNP with UtA blood flow and resistance. None of these

natriuretic peptides measured at 22-24 weeks gestation reflected cardiac preload reserve or predicted development of HDP.

Keywords

Maternal hemodynamics, Natriuretic peptides, Cardiac output, Preload reserve, Passive leg raising, Pregnancy, Preeclampsia, Uterine artery Doppler

Abbreviations:

ACI, Acceleration index

ANP, Atrial natriuretic peptide

BNP, Brain natriuretic peptide

BMI, Body mass index

CNP, C-type natriuretic peptide

CO, Cardiac output

CVP, Central venous pressure

HDP, Hypertensive disorders of pregnancy

ICG, Impedance cardiography

LVCWI, Left ventricular cardiac work index

LVET, Left ventricular ejection time

MAP, Mean arterial pressure

PEP, preejection period

PI, Pulsatility index

PLR, Passive leg raising

Quta, Uterine artery volume blood flow

SV, Stroke volume

SVR, Systemic vascular resistance

UtA, Uterine artery

VI, Velocity index

Key message: In pregnant women, natriuretic peptides measured at 22-24 weeks correlated with some parameters of baseline cardiovascular function, but did not reflect preload reserve and did not predict development of hypertensive disorders of pregnancy.

Introduction

Maternal cardiovascular remodeling is a physiological process required to adjust to the needs of the growing uterus, fetus and placenta. During pregnancy there is a substantial increase in circulating blood volume and cardiac output (CO), and a decrease in systemic vascular resistance (SVR). [1,2]

Passive leg raising (PLR), a maneuver of lifting the legs from the horizontal plane to 45° using a pivotable bed, provides a rapid reversible auto-fluid challenge by increasing venous return to the heart.[3] The homodynamic response to PLR can be used to assess preload reserve and functional hemodynamics.[4,5] By using this method, we have previously shown that pregnant women have a limited preload reserve.[6,7]

Atrial natriuretic peptide (ANP), brain natriuretic peptide(BNP) and C-type natriuretic peptide (CNP) are the most important members of the natriuretic peptide family that are involved in maintaining volume homeostasis and endothelial function. ANP and BNP are of myocardial origin,[8] and known to be produced in response to myocardial wall stress or pressure overload.[9] Pro-ANP and pro-BNP are the principal storage form of of these peptide hormones that are cleaved into the active hormones ANP and BNP and an inactive fragment, N-terminal (Nt)-proANP and Nt-proBNP, respectively. CNP is a paracine hormone produced by the endothelium in response to vascular stress.

In uncomplicated human pregnancies, ANP and BNP levels are similar or slightly higher compared with non-pregnant state, but remain stable throughout gestation.[10-12] Maternal plasma CNP is reduced in healthy pregnant women compared to non-pregnant women, and levels tend to fall with advancing gestation.[13] However, increased levels are found in pregnant women who later develop complications such as preeclampsia and/or fetal growth restriction.[14] Levels of all these natriuretic peptides are known to be increased in preeclamptic pregnancies.[14-16]

As the primary basis of their production during pregnancy is similar to that in non-pregnant women, ANP and BNP could be adopted as biomarkers of early cardiac dysfunction or volume overload during pregnancy. Similarly, CNP could be used as a marker of vascular endothelial dysfunction.

Both maternal systemic hemodynamic measurements and natriuretic peptide levels have been used to assess cardiac function in pregnancy. However, the association between maternal cardiovascular hemodynamics and natriuretic peptides has not been elucidated. Furthermore, both abnormal uterine artery (UtA) Doppler blood flow velocity waveforms[17] as well as vascular endothelial dysfunction[18] in the first or second trimester of pregnancy are known to be associated with later development of preeclampsia. However, whether UtA hemodynamics correlates with maternal CNP levels is not known. Thus, our primary objective was to investigate the association between maternal cardiac function, preload reserve, UtA hemodynamics and natriuretic peptides at 22-24 weeks of gestation.

Preeclampsia is known to be associated with cardiac dysfunction and remodeling.[19] Some researchers have found elevated natriuretic peptide levels in preeclampsia, [15,16,20] and others have reported that asymptomatic cardiac dysfunction may be detected at mid-gestation in women who subsequently develop preeclampsia.[21] Therefore, our secondary objective was to explore differences in maternal functional hemodynamics and natriuretic peptide levels between women who subsequently develop hypertensive disorders of pregnancy (HDP) and those who do not.

Material and methods

This study was conducted from January 2009 to November 2013. The primary objective of the study was assessed in a cross-sectional design, while the secondary objective was assessed in a prospective cohort design.

Pregnant women were informed about the study when they were attending the routine ultrasound screening at 17-20 weeks of gestation. Those women who agreed to participate and signed the informed consent were recruited consecutively and an appointment was made at 22-24 weeks of gestation for the evalaution of their cardiovascular function. These women were subsequently followed until delivery. Exclusion criteria were: age <18 years, chronic hypertension, multiple pregnancy and presence of any major fetal structural or chromosomal abnormalities.

The participanting women were examined in a fasting state, in a quiet room with stable temperature maintained at approximately 22°C. Height and weight were measured using an altimeter (Charder Electronic Co, Taichung City, Taiwan) and an

electronic scale (Soehnle, Leifheit AG, Nassau, Germany), respectively. The body mass index (BMI) was calculated as weight/height^2, and the body surface area (BSA) was calculated using the Du Bois formula[22] as: $BSA\ (m^2) = 0.007184 \times Height^{0.725} \times Weight^{0.425}$. The information on the course and outcome of pregnancy was obtained from the electronic hospital records. Gestational hypertension was defined as new-onset nonproteinuric hypertension (blood pressure ≥ 140/90 mmHg). Preeclampsia was defined as new-onset hypertension with proteinuria (≥1+ on a routine urinalysis or ≥ 300 mg/24 hours) or organ failure. HDP included both gestational hypertension and preeclampsia.

Cardiac function and preload reserve

Maternal cardiac function and systemic hemodynamics was investigated using ICG (Philips Medical Systems, Androver, MA, USA) as described previously.[6,7,23] ICG is a validated noninvasive technique[24] that allows continuous recording and on screen display of measured parameters. A single investigator (ÅV) performed all ICG measurements.

Woman's age, present weight and height were input into the ICG machine, central venous pressure (CVP) was preset at 4 mmHg and pulmonary artery occlusion pressure (PAOP) was preset at 8 mmHg. The following variables were continuously displayed on the ICG screen: cardiac output (CO),cardiac index (CI), heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), stroke volume (SV), stroke index (SI), thoracic fluid content (TFC)，systemic vascular resistance (SVR)，systemic vascular resistance index (SVRI), acceleration cardiac index (ACI), left ventricular cardiac work index (LCWI), pre-ejection period (PEP), left ventricular ejection time (LVET), and velocity index (VI). The mean arterial blood pressure (MAP) was calculated as DBP + 1/3 (SBP-DBP), SVR as (MAP-CVP)/CO x 80, and systolic time ratio (STR) as PEP/ LVET.

Baseline measurements were performed after approximately 10 minutes of rest with the pregnant woman lying in a 45° semi-recumbent position on an electronically pivotable bed. After the parameters were stabilized, baseline values were recorded. Then, the PLR maneuver was performed to assess preload reserve. The woman´s legs were raised from the horizontal plane up to 45° while the upper body was

lowered to a supine position electronically steering the pivotable bed without any movements performed by the woman herself. Another set of measurements was recorded 90 seconds after PLR. The woman was instructed to remain quiet during the whole procedure. The cardiovascular response to PLR was expressed as percent change (Δ%) of the hemodynamic variables from baseline to PLR, i.e. (measurement after PLR - measurement at baseline) / measurement at baseline x 100%. The preload reserve was defined as Δ % of SV and CO from baseline to PLR.

Uterine artery hemodynamics

UtA hemodynamics was assessed by Doppler ultrasonography using an Acuson Sequoia 512 ultrasound system (Mountain View, CA, USA). Two experienced operators (CW and KF) performed all ultrasound examinations following the ALARA (as low as reasonably achievable) principle[25] using the method described previously.[23,26-28] UtA was identified transabdominally using color Doppler and blood flow velocity waveforms were recorded from the left and right UtA using pulsed-wave Doppler keeping the insonation angle as low as possible (always <30 degrees). UtA blood flow velocities were measured online using the software of the ultrasound machine. The uterine artery pulsatility index (UtA PI) was calculated as follows: UtA PI = (peak systolic velocity - end-diastolic velocity)/ time-averaged maximum velocity. An average of 3 consecutive waveforms was used for analysis.

UtA diameter was measured using power Doppler angiography as described previously.[23,26,27] UtA blood flow volume (Quta) was calculated as: Quta = UtA time-averaged intensity weighted mean velocity x cross-sectional area of the UtA. The cross-sectional area was calculated as: 3.14x (UtA diameter/2)^2. Total Quta was calculated as the sum of the left and the right Quta.

The UtA resistance (Ruta) was calculated as: Ruta = MAP/total Quta.[27] The fraction of maternal CO distributed to the uterus was calculated as total Quta/CO as described previously.[29]

Natriuretic peptides

Maternal fasting blood samples were obtained for analysis of the natriuretic peptides. A vacuette tube was used for collecting venous blood by venipuncture of the

antecubital vein. Peripheral blood was collected in ethylenediaminetetraacetic acid (EDTA) and serum tubes. EDTA plasma and serum were separated by centrifugation at room temperature for 10 minutes at 1250 g, transferred to cryotube (Sigma Aldrich Gmbh, Munich, Germany) and then immediately frozen at -70°C until analysis of natriuretic peptides was performed.

Enzyme-linked Immuno-sorbent assay (ELISA) kits were used for quantification of natriuretic peptides according to the manufacturer's instructions. EDTA plasma samples were used for the analysis of pro-ANP and CNP, whilst BNP was quantified in serum samples. The intra-assay coefficient of variation (CV) for pro-ANP ELISA kit (EIA-4703, DRG, Instruments, GmbH, Germany) was ≤5%, and the inter-assay CV was ≤9% and sensitivity (0 pmol/L +3SD).

Nt-proBNP was quantified using a direct ELISA kit (EIA-4827, DRG Instruments, GmbH, Germany) that had an intra-assay CV of ≤4%, the inter-assay CV of ≤7% and sensitivity (0 pmol/L + 3SD): 3 pmol/L, detection range 0 – 640 pmol/L.
CNP was analyzed using a human C-type natriuretic peptide kit (CSB-E08909h, CUSABIO, Lab-Tech AS, Norway) that had an intra-assay CV of ≤8%, the inter-assay CV of ≤10%, and detection range 62.5 - 4000 pg/ml.

Statistical analyses

Data were analyzed using IBM SPSS statistics (SPSS software, version 24.0.0, Chicago, IL, USA). Variables were presented as mean (±SD), median (range) or n (%) as appropriate. Statistical significance was set as a two-sided p-value of <0.05. Assumption of normality was checked for each variable using Shapiro-Wilk test. When the variables could be assumed to be normally distributed, independent sample t-test was used for comparison between reference group and HDP group, and paired-sample t-test was used for comparison between measurements obtained on the same women at baseline and 90s after PLR. When the variables were not normally distributed, nonparametric Wilcoxon test was used. Chi-square test was applied for the analysis of differences in proportions between groups. Nonparametric Spearman rank correlation test was used to assess correlation of natriuretic peptides, which were not normally distributed, with variables describing maternal cardiac function, systemic hemodynamics and uterine artery hemodynamics.

Ethical approval:

The study protocol was approved by the Regional Committee for Medical and Health Research Ethics - North Norway (Ref.nr. 5.2005.1386. Date of approval: 12.03.2010).

Results

Of a total of 350 pregnant women recruited to the study, three were excluded because of missing blood samples and 347 were included in the final statistical analysis. Thirty-three (9.5%) women developed HDP later in the pregnancy (17 cases of gestational hypertension and 16 cases of preeclampsia), 80.7% had an uncomplicated vaginal delivery, 5.8% had an operative vaginal delivery and 13.5% were delivered by cesarean section. Twenty-one women delivered pre-term: 10 in the reference group (10/312, 3.2%) and 11 in the HDP group (11/33, 33.3%) ($p<0.001$). The differences in baseline characteristics between the reference group and the HDP group are presented in Table 1. There was no significant difference in maternal age ($p =0.459$), but the HDP group had significantly higher BMI ($p=0.010$) and MAP ($p<0.001$). The HDP group delivered earlier in gestation ($p=0.008$), and had lower birthweight babies ($p=0.002$) with lower 5-minute Apgar score ($p=0.001$) and lower placental weight ($p=0.036$).

Maternal cardiac function and systemic hemodynamic measurements obtained at baseline and 90 seconds after PLR are shown in Table 2. At baseline, ProANP correlated significantly with CO ($r= -0.122$; $p=0.023$) and LCWI ($r= -0.112$; $p=0.037$). Nt-proBNP correlated significantly with ACI ($r=0.127$; $p=0.018$) and VI ($r= -0.111$; $p=0.039$). CNP correlated significantly with Quta ($r=0.118$; $p=0.028$) and Ruta ($r= -0.112$; $p=0.037$) but not with UtA PI ($r=0.034$; $p=0.523$).

During PLR, ProANP correlated significantly with Δ % DBP ($r= -0.124$; $p=0.021$), Δ % MAP ($r= -0.142$; $p=0.008$) , Nt-ProBNP correlated significantly with Δ % DBP ($r= -0.134$; $p=0.013$). However, none of the natriutetic peptides correlated significantly with preload reserve.

Women who subsequently developed HDP had significantly higher increase in SV and CO and more reduction in SVR following PLR compared with the reference group. ACI, VI and LCWI decreased following PLR in the reference group, whereas they increased in women who later developed HDP.

Maternal UtA hemodynamics and natriuretic peptide levels in reference group and HDP group are presented in Table 3. At 22-24weeks, women who subsequently developed HDP had higher mean UtA PI (1.12 vs. 0.84; p<0.001), lower total Quta (552 vs. 692 ml/min; p=0.028) and higher Ruta (0.28 vs. 0.17mmHg/mL/min; p=0.004) compared to those who did not, but had similar natriuretic peptide levels.

Discussion

In this study we evaluated whether there is an association between maternal natriuretic peptides and cardiovascular function in pregnant women at 22-24 weeks of gestation and explored differences between women who had normal pregnancy outcome and those who subsequently developed HDP. We observed that none of the natriuretic peptides reflected maternal cardiac preload reserve or predicted development of HDP in the third trimester of pregnancy. ProANP correlated with CO, a major determinant of global oxygen delivery, but Nt-proBNP did not. However, both ProANP and Nt-proBNP correlated with cardiac work (LCWI). CNP correlated with UtA blood flow and resistance but not with maternal cardiac function. Women who developed HDP later in pregnancy had significantly higher increase in SV and CO and more reduction in SVR following PLR compared with the reference group. The varibles describing cardiac contractilty and work (ACI, VI and LCWI) decreased in the reference group after PLR whereas they increased in women who later developed HDP.

Cardiac function is affected by pregnancy due to an increase in preload and a decrease in afterload, and these changes are clearly evident by mid-gestation, but the preload reserve, i.e. the ability of the heart to increase its output in response to a rapid transient increase in venous return, is limited in the second half of pregnancy,[6,7] most likely due to cardiovascular remodeling as a result of increased volume load. When the heart has adapted to chronic volume load, as in normal pregnancy, there is still a perfect match of afterload with inotropic state, but with essentially maximum use of preload. Therefore, with limited preload reserve a mismatch between afterload and inotropic state can happen. As a result, with increasing afterload, the LV may not be able to maintain its SV when preload is fully utilized (i.e. the limit of the preload reserve is reached).[30,31] Hameed et al.[11] have shown that BNP levels are approximately two-fold higher in pregnant women compared to non-pregnant women

and they do not significantly fluctuate. NT-proBNP appears to increase until mid-pregnancy, suggesting a correlation with volume expansion,[32] and probably reflecting the physiological increase in CO during pregnancy. However, in our study, the Nt-proBNP levels measured at 22-24 weeks did not correlate with CO, but ProANP, which is known to increase with myocardial stress, had a negative correlation with CO and LCWI suggesting that volume overload may negatively effect cardiac performance in pregnancy.

The circulatory volume is usually reduced in women with HDP, and untreated patients with preeclampsia who have increased SVR respond to plasma volume expansion by increasing their CO.[33] In our cohort, women who developed HDP later in gestation, increased their SV and CO, and improved their ICG-derived indices of cardiac contractility during PLR at 22-24 weeks, suggesting that these women might be slightly volume depleted already in mid-gestation due to an inadequate increase in plasma volume. Therefore, their heart responds to small increase in preload caused by transient increase in venous return as a result of PLR.

Hemodynamics is generally expressed as flow-pressure relationship, although it is the flow component that continuously adapts to the changing demands of the tissues and organs for oxygen delivery. At baseline, proANP correlated negatively with CO and LCWI, NT-ProBNP correlated positively with ACI and VI, whereas CNP didn't correlate with any of the parameters of cardiac function measured by ICG. None of the natriuretic peptides correlated with change in SV or CO caused by PLR, suggesting that they do not reflect preload reserve in pregnant women during 22-24 weeks of gestation. Although ProANP and NT-ProBNP correlated negatively with Δ % BPD and proANP correlated negatively with Δ % MAP, no significant correlation was found between these natriuretic peptides and Δ % SVR suggesting that the reduction in SVR following volume expansion observed in preeclamptic women[33] may be a result of improved cardiac performance rather than afterload reduction.

It is known that second trimester abnormal UtA Doppler velocity waveform is associated with increased risk of developing HDP later in pregnancy.[17] As expected, in our study, women who developed HDP in the third trimester had higher UtA PI, lower Quta and higher Ruta at 22-24 weeks. Interestingly, ANP and BNP did not correlate with UtA hemodynamics but CNP correlated positively with UtA blood flow and negatively with UtA resistance. This supports the hypothesis that CNP levels

reflect uterine vascular endothelial dysfunction, which may precede the development of HDP. In our study, CNP did not significantly correlate with UtA PI. This is not surprising as UtA PI, although considered a surrogate measure of utero-placental impedance, does not always reflect the Ruta[34] or maternal endothelial function.[23]
Untreated women with HDP, especially those with placental insufficiency, have high SVR and low cardiac index,[35,36] and plasma levels of ANP and BNP are reported to be higher in preeclamptic women compared to normotensive pregnant women.[15,16,20] Furthermore, ANP and BNP are shown to be linearly related to the left ventricular structural and functional changes observed in women with preeclampsia.[37] However, whether these natriuretic peptides are more sensitive markers of cardiac dysfunction in pregnancy compared to other parameters of cardiovascular function, is not known. Using tissue Doppler and strain rate analysis, asymptomatic cardiac diastolic dysfunction has been reported to be present at 20-23 weeks of gestation in women who subsequently develop preterm preeclampsia requiring delivery before 37 weeks.[21] In our study, natriuretic peptide levels at 22-24 weeks were similar among women who subsequently developed HDP and those who did not. However, due to a small number of women that developed preeclampsia, subgroup analysis stratifying different types of HDP was not possible, and the value of mid-gestation maternal ANP and BNP in predicting HDP remains unclear.
Significantly elevated tissue Doppler E/E´ ratio has been reported in preeclamptic compared to the normotensive pregnant women. This increase has been attributed to a rise in the tissue Doppler early filling wave (E´) and has been suggested to reflect rising cardiac filling pressures in preeclampsia.[38] However, it has been shown that preeclamptic women are preload responsive, i.e. they increase their CO in response to volume load.[33,39] Although in clinical practice pulmonary artery occlusion pressure is considered to reflect preload (pressure is easier to assess than the flow and volume), preload is related to filling blood volume rather than the filling pressure; and left atrial and ventricular pressures are a function of blood inflow and chamber compliance. Pregnant women, who are generally young, have a complaint ventricular wall and can be volume overloaded despite normal filling pressures.

A strength of our study is its relatively large sample size. To our knowlege it is the largest study so far evaluating maternal cardiac function, using ICG and natriuretic peptides in the same pregnant population. In addition, we studied UtA

hemodynamics and correlated it with CNP, a known marker of vascular endothelial function. There are no previoius studies that have simultaneously evaluated CNP and UtA blood flow during pregnancy. However, the number of participants included was not sufficient to draw definitive conclusions regarding predictive value of mid-gestaion maternal functional hemodynamics and natriuretic peptides in predicting subsequent development of HDP. Similarly due to small number of cases with HDP, subanalysis by stratification into different types of HDP (such as early and late onset) was not possible.

Although the values of natriuretic peptides are reported to be stable during pregnacy, the cross-sectional design of our study does not allow us to draw conclusions regarding temporal changes in natriuretic peptide levels and their association with maternal functional hemodynamics throughout the pregnancy. Ethnic differences in BNP have been reported in term pregnancies,[12] and as our study population consisted mainly of homogenous North European women, the findings may not be generalizable to other ethnic populations.

Conclusions

ProANP correlated with CO and cardiac work, Nt-proBNP with indices of cardiac contractility, and CNP with UtA blood flow and resistance. None of these natriuretic peptides measured at 22-24 weeks of gestation reflected cardiac preload reserve or predicted development of HDP. There appears to be no additional clinical value of measuring natriuretic peptides to screen pregnant women in the second trimester for subsequent development of HDP. However, larger studies are needed to confirm these findings.

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