Ultrasound Obstet Gynecol 2017; **50**: 584–588
Published online in Wiley Online Library (wileyonlinelibrary.com). **DOI:** 10.1002/uog.17379

Screening for pre-eclampsia in the first trimester: role of maternal hemodynamics and bioimpedance in non-obese patients

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KEYWORDS: bioimpedance; cardiac function; combined screening; first trimester; hemodynamics; pre-eclampsia

ABSTRACT

Objective *To test if maternal hemodynamics and bioimpedance, assessed at the time of combined screening for PE, are able to identify in the first trimester of gestation normotensive non-obese patients at risk for pre-eclampsia (PE) and/or intrauterine growth restriction (IUGR).*

Methods *One hundred and fifty healthy nulliparous non-obese women (body mass index $< 30\,kg/m^2$) in the first trimester of pregnancy underwent assessment by UltraSonic Cardiac Output Monitor (USCOM) to detect hemodynamic parameters, bioimpedance analysis to characterize body composition, and combined screening for PE (assessment of maternal history, biophysical and maternal biochemical markers). Patients were followed until term, noting the appearance of PE and/or IUGR.*

Results *One hundred and thirty-eight patients had an uneventful pregnancy (controls), while 12 (8%) developed complications (cases). USCOM showed, in cases compared with controls, lower cardiac output (5.6 ± 0.3 vs 6.7 ± 1.1 L/min, $P < 0.001$), lower inotropy index (1.54 ± 0.38 vs 1.91 ± 0.32 W/m^2, $P < 0.001$) and higher total vascular resistance (1279.8 ± 166.4 vs 1061.4 ± 179.5 dynes × s/cm^5, $P < 0.001$). Bioimpedance analysis showed, in cases compared with controls, lower total body water ($53.7 \pm 3.3\%$ vs $57.2 \pm 5.6\%$, $P = 0.037$). Combined screening was positive for PE in 8% of the controls and in 50% of the cases ($P < 0.001$). After identification of cut-off values for USCOM and bioimpedance parameters, forward multivariate logistic regression analysis identified as independent predictors of complications in pregnancy the inotropy index (derived by USCOM), fat mass (derived from bioimpedance analysis) and combined screening.*

Conclusions *Combined screening for PE and assessment of bioimpedance and maternal hemodynamics can be used to identify early markers of impaired cardiovascular adaptation and body composition that may lead to complications in the third trimester of pregnancy.*

INTRODUCTION

The maternal cardiovascular system adapts to pregnancy by means of complex physiological mechanisms that involve cardiac output (CO), total vascular resistance (TVR) and body-water distribution. In particular, there is a decline in TVR followed by an increase in CO and changes in body composition. These changes occur early in pregnancy[1,2] and remain in the second and third trimesters.

There is a strict correlation between total body water (TBW) and plasma volume in physiological pregnancy. Abnormalities of adaptive mechanisms may result in hypertensive disorders and intrauterine growth restriction (IUGR)[3]. In recent years, studies have shown the importance of maternal hemodynamic assessment for the identification of patients at risk for pre-eclampsia (PE) during the second trimester of pregnancy[4]. In addition, women who develop hypertensive complications during pregnancy have an inappropriate increase in intracellular (ICW) and extracellular (ECW) water concentrations[5]. Therefore, maternal hemodynamic and body-composition assessment in early pregnancy might be important in identifying patients at risk for PE and/or IUGR.

Several studies have been directed at early evaluation of maternal adaptation, focusing on analysis of placental

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Accepted: 25 November 2016

markers and uterine artery Doppler, which are indicative of placental impairment linked to inadequate trophoblastic invasion of the maternal spiral arteries. This leads to placental ischemic damage and release of inflammatory factors, platelet activation and endothelial injury[6], which are apparently associated with the subsequent development of PE. Poon and Nicolaides[7] analyzed placental perfusion and pregnancy-related proteins in the first trimester of pregnancy, showing how combined screening for PE, including maternal history, biophysical markers (uterine artery Doppler and arterial blood pressure) and maternal biochemical markers (serum pregnancy-associated plasma protein-A (PAPP-A) and placental growth factor (PlGF)), has a detection rate for risk of PE of about 95% in the first trimester[7].

The aim of this study was to test in non-obese patients the usefulness of different hemodynamic parameters obtained by USCOM (UltraSonic Cardiac Output Monitor) and bioimpedance analysis, performed at the time of combined screening (assessment of biochemical serum markers associated with maternal factors, blood pressure and uterine artery Doppler), in order to identify the best predictive variables in the first trimester of pregnancy for the risk of PE and/or IUGR.

METHODS

This was a prospective observational study at the Department of Obstetrics and Gynaecology, Casilino Hospital, Rome, over a continuous period from January 2014 to February 2016. We enrolled 160 healthy women between 11 + 0 weeks and 13 + 6 weeks. Inclusion criteria were: nulliparity, normal blood pressure at enrolment, singleton pregnancy, certain date of pregnancy, normal fetal parameters at enrolment, absence of maternal disease and body mass index (BMI) < 30 kg/m^2 at enrolment. Exclusion criteria were: undetermined gestational age, tobacco use, multiple pregnancy, pre-existing chronic maternal disease, use of medication other than iron supplements and conception following assisted reproductive techniques.

For the hemodynamic assessment, measurements were obtained using the USCOM system. USCOM is a non-invasive Doppler method to determine hemodynamic values. A non-imaging continuous-wave Doppler transducer is placed on the suprasternal notch to determine transaortic blood flow. After entering manually into the system the woman's blood pressure, weight and height, USCOM is able to calculate the following cardiovascular parameters: stroke volume (SV), CO, heart rate (HR), TVR, inotropy index (INO) and time flow correct (TFC)[8]. After USCOM measurements were obtained, systolic (SBP) and diastolic (DBP) blood pressure were measured from the brachial artery with an automatic blood pressure monitor (Microlife, Microlife AG, Widnau, Switzerland), with automated calculation of three consecutive measurements from both arms. Mean blood pressure (MBP) was calculated according to the formula: MBP = DBP + (SBP – DBP)/3. TVR in dynes × s/cm^5 was calculated automatically by USCOM after the introduction of SBP and DBP according to the following formula: TVR = (MBP (mmHg)/CO (L/min)) × 80.

Bioimpedance analysis was used to characterize body composition, based on the conductance of an alternating electrical current through the body tissues. The device, a BIA RJL Systems 101 S (Akern, Florence, Italy), utilizes a tetrapolar impedance plethysmograph with four electrodes placed on the skin surface. Impedance was measured at 50 kHz and the Lukaski[9] and Segal[10] formulae were applied to calculate TBW, ICW, ECW and fat mass (FM).

For combined screening, medical history was taken, mean uterine artery pulsatility index (PI) and MBP were calculated, and PAPP-A and PlGF plasma levels were measured. All of these parameters were expressed in multiples of the median (MoM), and the risk for PE was calculated using the Pre-Eclampsia Predictor software program (PerkinElmer®), as described by Poon and Nicolaides[7].

Pregnancies were followed until term and were classified as either uncomplicated (controls) or complicated (cases) if PE and/or IUGR developed before 34 weeks' gestation. The criteria of the International Society for the Study of Hypertension in Pregnancy[11] were used to define PE. This was diagnosed if a previously normotensive woman had two consecutive (4 h apart) DBP measurements > 90 mmHg after the 20th week of gestation, and proteinuria > 300 mg in a 24-h urine specimen. IUGR was defined as birth weight < 10th percentile with umbilical artery PI > 95th percentile[12].

To test intraobserver and interobserver variability of USCOM measurements, two independent observers measured SV in 20 arbitrarily selected patients. The measurements were repeated by one of the two observers.

Statistical analysis

Clinical data were expressed as mean ± SD. Comparisons between controls and cases were performed with Student's *t*-test for unpaired data. Differences were considered as significant when $P < 0.05$. For each continuous parameter, univariate binary logistic regression analysis was performed to identify variables predictive of complications. To compare the predictivity of bioimpedance and USCOM parameters with that of combined screening (a categorical variable), a receiver–operating characteristics (ROC) curve was constructed for each bioimpedance and USCOM parameter, to identify the best cut-off and convert the parameters into categorical variables. Univariate binary logistic regression analysis was performed and odds ratios (ORs) were calculated. Since CO, cardiac index (CI), HR and blood pressure values were included in the TVR formula, and are related to each other, only TVR was included in the multivariate binary logistic regression analysis. Similarly, PAPP-A, PlGF, uterine artery PI, MBP and anamnestic records were excluded from the multivariate binary logistic regression analysis, since these were included in the combined screening. Therefore, forward multivariate binary logistic regression analysis was

performed including the categorical variables TVR, TBW, ECW, ICW, FM, INO, TFC and combined screening; variables were entered into the statistical model if $P < 0.05$ and removed if $P > 0.1$. For the investigation of repeatability of USCOM measurements (SV), we calculated the coefficient of variation.

RESULTS

We enrolled 160 patients, of whom 10 were lost to follow-up. Among the remaining 150 patients, 12 (8%) developed pregnancy complications (two cases of early PE, three of PE with IUGR and seven of IUGR). The two groups, 12 cases and 138 controls, were not significantly different in age or BMI at the time of the first assessment (Table 1). Birth weight and birth-weight centile as well as gestational age at delivery were significantly lower in cases compared with controls.

CO and INO were lower, and TVR was higher, in cases compared with controls ($P < 0.001$) (Table 2). There was no statistically significant difference, in terms of MoM, between cases and controls for MBP (1.11 ± 0.14 *vs* 1.08 ± 0.10 MoM, $P = 0.08$), uterine artery Doppler (PI) (0.60 ± 0.29 *vs* 0.72 ± 0.29 MoM, $P = 0.167$) and PAPP-A (0.77 ± 0.30 *vs* 1.09 ± 0.65 MoM, $P = 0.095$), while PlGF was significantly lower in cases compared with controls (0.65 ± 0.20 *vs* 0.87 ± 0.37 MoM, $P = 0.028$). TBW was significantly lower in cases *vs* controls, whereas there was no difference between the groups for ECW, ICW or FM (Table 2).

Figures S1 to S9 show the ROC curves for TVR, INO, TFC, FM, CO, CI, TBW, ECW and ICW, and Table 3 summarizes the predicitive performance of these parameters at optimal cut-offs. Table 4 reports the univariate logistic regression analysis for each continuous and categorical (after identification of the cut-off through the ROC-curve analysis) variable, and Table 5 presents ORs from the multivariate logistic regression analysis. Independent predictors for pregnancy complications were: INO, FM and combined screening.

Intra- and interobserver variability for SV obtained using USCOM in terms of coefficient of variation were 6.0% ($r = 0.98$) and 6.4% ($r = 0.97$), respectively.

Table 1 Baseline characteristics of study population of healthy nulliparous non-obese women, according to whether pregnancy was uneventful (controls) or developed complications (cases)

	Controls (n = 138)	*Cases (n = 12)*	P
BMI (kg/m^2)	22.1 ± 3.4	22.7 ± 1.2	0.553
Age (years)	34 ± 5	35 ± 5	0.615
Birth weight (g)	3340 ± 463	1790 ± 403	< 0.001
Birth-weight centile	55 ± 20	10 ± 6	< 0.001
GA (weeks)	39 ± 1	35 ± 2	< 0.001

BMI, body mass index; GA, gestational age at delivery.

Table 3 Summary of predictive performance of optimal cut-off values for hemodynamic and bioimpedance parameters, derived from receiver–operating characteristics curve analysis

Variable	*Cut-off*	*Sens (%)*	*Spec (%)*
TVR (dynes × s/cm^5)	> 1130	91.7	74.6
INO (W/m^2)	< 1.5	75.0	80.4
TFC (ms)	> 401	50.0	87.0
FM (%)	≤ 20	75.0	67.4
CO (L/min)	≤ 6.1	100.0	67.4
CI (L/min/m^2)	≤ 3.2	50.0	91.3
TBW (%)	≤ 54.4	75.0	73.9
ECW (%)	≥ 42.8	75.0	63.0
ICW (%)	≤ 56.9	75.0	63.0

CI, cardiac index; CO, cardiac output; ECW, extracellular body water; FM, fat mass; ICW, intracellular body water; INO, inotropy index; sens, sensitivity; spec, specificity; TBW, total body water; TFC, time flow correct; TVR, total vascular resistance.

Table 2 Hemodynamic and bioimpedance features and combined screening results, at 11–13 weeks' gestation, of healthy nulliparous non-obese women, according to whether pregnancy was uneventful (controls) or developed complications (cases)

	Controls (n = 138)	*Cases (n = 12)*	P
SBP (mmHg)	117 ± 10	120 ± 16	0.09
DBP (mmHg)	71 ± 7	75 ± 7	0.01
MBP (mmHg)	86 ± 7	90 ± 10	0.02
CO (L/min)	6.7 ± 1.1	5.6 ± 0.3	< 0.001
CI (L/min/m^2)	4.0 ± 0.6	3.7 ± 0.6	0.056
HR (bpm)	78 ± 11	75 ± 4	0.497
TVR (dynes × s/cm^5)	1061.4 ± 179.5	1279.8 ± 166.4	< 0.001
INO (W/m^2)	1.91 ± 0.32	1.54 ± 0.38	< 0.001
TFC (ms)	374.9 ± 98.0	381.0 ± 22.0	0.479
TBW (%)	57.2 ± 5.6	53.7 ± 3.3	0.037
ECW (%)	42.0 ± 3.8	41.1 ± 2.1	0.336
ICW (%)	58.0 ± 3.8	57.0 ± 2.1	0.336
FM (%)	22.6 ± 7.1	22.6 ± 5.4	0.915
Combined screening* (% (*n*))	8 (15)	50 (6)	< 0.001

Data are given as mean ± SD unless stated otherwise. *Based on maternal history and biochemical (pregnancy-associated plasma protein-A and placental growth factor) and biophysical (uterine artery pulsatility index, mean blood pressure (MBP)) markers calculated with Pre-Eclampsia Predictor software program (PerkinElmer®). CI, cardiac index; CO, cardiac output; DBP, diastolic blood pressure; ECW, extracellular body water; FM, fat mass; HR, heart rate; ICW, intracellular body water; INO, inotropy index; SBP, systolic blood pressure; TBW, total body water; TFC, time flow correct; TVR, total vascular resistance.

Table 4 Univariate binary logistic regression analysis with continuous and categorical variables after identification by receiver–operating characteristics curve of cut-off for each parameter for the prediction of pregnancy complications in healthy nulliparous non-obese women

Continuous variables			*Categorical variables*		
Variable	*OR (95% CI)*	P	*Variable*	*OR (95% CI)*	P
TVR (dynes × s/cm^5)	1.006 (1.003–1.009)	0.001	TVR > 1130 dynes × s/cm^5	11.276 (2.867–44.345)	< 0.0001
INO (W/m^2)	0.018 (0.002–0.206)	0.001	INO < 1.5 W/m^2	12.333 (3.126–48.666)	< 0.0001
TFC (ms)	1.008 (0.986–1.030)	0.476	TFC > 401 ms	6.667 (1.938–22.929)	0.003
FM (%)	1.000 (0.919–1.089)	0.995	FM ≤ 20%	6.200 (1.600–24.018)	< 0.0001
HR (bpm)	0.979 (0.921–1.041)	0.494	HR ≤ 80 bpm	0.457 (0.096–2.177)	0.291
CO (L/min)	0.237 (0.098–0.573)	0.001	CO ≤ 6.1 L/min	25.140 (3.144–201.06)	0.002
CI (L/min/m^2)	0.356 (0.122–1.039)	0.059	CI ≤ 3.2 L/min/m^2	10.500 (2.928–37.658)	0.0003
TBW (%)	0.895 (0.804–0.996)	0.412	TBW ≤ 54.4%	8.500 (2.180–33.144)	< 0.0001
ECW (%)	1.101 (0.909–1.334)	0.324	ECW ≥ 42.8%	4.667 (1.209–18.013)	0.026
ICW (%)	0.908 (0.750–1.100)	0.324	ICW ≤ 56.9%	5.118 (1.325–19.773)	0.018
BMI (kg/m^2)	1.051 (0.893–1.237)	0.551	BMI > 21.5 kg/m^2	0.218 (0.046–1.033)	0.055
			Combined screening	8.200 (2.344–28.682)	< 0.001

BMI, body mass index; CI, cardiac index; CO, cardiac output; ECW, extracellular body water; FM, fat mass; HR, heart rate; ICW, intracellular body water; INO, inotropy index; OR, odds ratio; TBW, total body water; TFC, time flow correct; TVR, total vascular resistance.

Table 5 Independent predictors of pregnancy complications in healthy nulliparous non-obese women identified at forward multiple binary logistic regression analysis of categorical variables

Variable	*OR (95% CI)*	P
Combined screening	21.4658 (3.3882–135.9968)	0.0011
FM ≤ 20%	11.5804 (1.9765–67.8519)	0.0066
INO < 1.5 W/m^2	17.0537 (3.2292–90.0629)	0.0008

FM, fat mass; INO, inotropy index; OR, odds ratio.

DISCUSSION

This study highlights the importance of hemodynamic and body-composition parameters in the identification of patients at risk for PE and/or IUGR in the first trimester. In particular, FM ≤ 20% at bioimpedance analysis and INO < 1.5 W/m^2 identified by USCOM appear to be independent predictors of these pregnancy complications.

Screening for PE in the first trimester of pregnancy is important because it identifies patients who will need very particular antenatal care. Combined screening, based on maternal history, biochemical (PAPP-A and PlGF) and biophysical (uterine artery Doppler, MBP) markers, has a high detection rate[7]. However, this test does not incorporate maternal hemodynamic parameters such as TVR, CO and INO, parameters that recent studies have shown to be significant for the screening and selection of patients with PE[13,14]. Hemodynamic changes, especially during the first weeks of pregnancy, and changes in body-water distribution, as assessed by TBW, ICW and ECW, can provide important information about maternal physiological adaptation to pregnancy. Indeed, several studies have shown that, in women who develop hypertensive complications in pregnancy, there is an altered distribution of ICW and ECW[5]. After identification of the cut-off values for TBW, ECW and ICW, we found, on univariate regression analysis, that low TBW and ICW and high ECW in the first trimester were predictive of complications, confirming the previous observations. Another peculiar result is the importance of FM after identification of the cut-off. In particular, while FM does not appear to be a predictor of complications as a continuous variable, once a cut-off had been identified (FM ≤ 20%), it became a strong predictor of complications both on univariate analysis and on multivariate forward regression analysis. Therefore, bioimpedance, through FM, can identify patients who show body constitutional characteristics indicative of early PE better than can isolated BMI, which was not a significant variable in this population.

In our study, patients who subsequently developed PE showed, even during the first trimester, higher TVR and lower CO and INO compared with patients whose pregnancy remained uneventful. In fact, data in the literature show that, in normal pregnancy, an increase in CO, with a decline in MBP, leads to a reduction in systemic vascular resistance[1,2]. The hemodynamic pattern of our cases is characteristic of cardiovascular maladaptation, with low levels of CO and INO and high TVR. INO represents cardiac contractility; therefore, a low INO value is indicative of decreased cardiac performance due to the inability of the myocardium to face the increased afterload; for the same reason, the TFC, which represents the systolic ventricular time, is apparently a predictor of complications on univariate analysis, when it is > 401 ms.

Our data confirm the findings of Kager *et al.*[15], who reported in healthy pregnant women a TVR value of 1030 ± 181 dynes × s/cm^5 in the first trimester. Our group with uncomplicated pregnancy had a TVR of 1061 ± 180 dynes × s/cm^5. The novel finding in our study is the significant difference in TVR values (1280 ± 166 dynes × s/cm^5) in the population which went on to develop a complication of pregnancy. Although our population was small, we also identified a cut-off of >1130 dynes × s/cm^5 as a strong predictor of complications in the univariate analysis. These cut-off values should be confirmed in larger populations.

Another important predictor of pregnancy complications was CO, which was lower in first-trimester pregnancies subsequently complicated by PE and/or

IUGR compared with the uncomplicated ones. The mean value of CO in our physiological population was again similar to that described by Kager *et al.*[15].

The most striking novel result of our study is the strong predictive value of INO and FM in the first trimester for subsequent complications in pregnancy. These two parameters, as well as combined screening, were predictive on both univariate and multivariate analysis, suggesting the importance of determination of hemodynamic features (by USCOM) and body composition (through bioimpedance assessment) in the first trimester as part of the risk assessment for subsequent complications of pregnancy.

Strengths of this study include the testing of several different parameters, and the identification in the first trimester of pregnancy of cut-off values for USCOM and bioimpedance variables. Another strength relates to the exclusion of obese women, for whom hemodynamics might be altered, particularly in the early phases of pregnancy. One might argue that exclusion of patients with a BMI $\geq 30\,kg/m^2$ was a weakness, because these patients are indeed at increased risk of PE. However, in these patients, the pathophysiology of PE is linked more closely to diffuse visceral phlogosis than to hypovolemia/reduced CO, so we feel our choice to exclude them was justified.

In conclusion, the purpose of this preliminary study was to test the usefulness of hemodynamic parameters derived by USCOM and body composition parameters derived by bioimpedance analysis in the first trimester of pregnancy for the prediction of PE and/or IUGR. We found that both bioimpedance analysis and assessment by USCOM, as well as combined screening, can identify early markers of impaired cardiovascular adaptation and body composition that may lead to complications in the third trimester. In particular, the USCOM parameter INO and the bioimpedance parameter FM were found to be independent predictors of PE and/or IUGR, as was combined screening for PE. Larger studies are needed to confirm the usefulness of these techniques and the cut-off values that we identified for this particular sample of patients, as well as their applicability in obese patients.

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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Figures S1–S9 Receiver–operating characteristics curves for identification of optimal cut-offs for total vascular resistance (Figure S1), inotropy index (Figure S2), time flow correct (Figure S3), fat mass (Figure S4), cardiac output (Figure S5), cardiac index (Figure S6), total body water (Figure S7), extracellular body water (Figure S8) and intracellular body water (Figure S9) for prediction of pregnancy complications in healthy nulliparous non-obese women.