Full length article

Non-invasive cardiac output monitoring (NICOM®) can predict the evolution of uteroplacental disease—Results of the prospective HANDLE study

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A B S T R A C T

Objectives: We aimed to firstly identify the different haemodynamic profiles amongst nulliparous women who develop either gestational hypertension (GH), preeclampsia (PE), normotensive fetal growth restriction (FGR) versus unaffected pregnancies using non-invasive cardiac output monitoring (NICOM®). Our second primary objective was to assess the ability of NICOM® derived variables to predict the evolution of PE, GH and FGR.

Study design: Low risk nulliparous women were enrolled in a single center prospective observational study. NICOM® assessments were performed at 14, 20 and 28 weeks’ gestation and data was obtained on cardiac output (CO), total peripheral resistance (TPR), indexed TPR (adjusted for maternal body surface area; TPRi), stroke volume (SV), indexed SV (adjusted for maternal body surface area; SVi) and heart rate (HR). Logistic regression was used to model GH, PE and FGR with NICOM® measurements as predictors. Linear, non-linear and interaction terms were assessed using the Akaike Information Criterion.

Results: The haemodynamic profile of pregnancies complicated by uteroplacental disease- GH (n = 18), PE (n = 6) and FGR (n = 24) were compared to 318 healthy unaffected pregnant controls. Women with evolving PE have a different haemodynamic profile to those developing either GH or FGR. The best independent predictors for the evolution of uteroplacental disease at 14 weeks’ gestation were CO in the prediction of FGR (AUC = 0.61; p < 0.002), TPR in the prediction of GH (AUC = 0.63; p < 0.02) and SVi in the prediction of PE (AUC = 0.62; p < 0.05). The performance of haemodynamic variables was enhanced when combined in a multivariate logistic model. We demonstrated that TPR, CO and SV when combined with BP were significant predictors of pregnancies complicated by FGR (AUC = 0.64, p = 0.004; AUC = 0.65, p = 0.004; and AUC = 0.65, p = 0.007 respectively). Whereas in pregnancies complicated by PE, HR and SVi in combination with BP were also statistically significant predictors (AUC = 0.75, p = 0.017 and AUC = 0.77, p = 0.007 respectively).

Conclusions: NICOM® derived maternal haemodynamic profile at 14 weeks’ gestation has the novel potential to identify pregnancies which will ultimately develop uteroplacental disease.

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Introduction

Preeclampsia (PE) & fetal growth restriction (FGR) account for a significant proportion of perinatal morbidity and mortality currently encountered in obstetric practice [1,2]. The primary goal of antenatal care is the early recognition of such conditions to allow treatment and optimization of both maternal and fetal outcomes. Hypertensive disorders of pregnancy are thought to
complicate approximately 10% of all pregnancies and PE is thought to affect between 2 and 8% of all pregnancies worldwide [3]. Despite an improvement in maternal outcomes, PE remains one of the leading direct causes of maternal deaths and is thought to be predominantly a result of impaired placentation [2,4]. The antenatal detection of FGR via clinical examination is suboptimal with a reported detection rate of one in three [5–7]. As a result many pregnancies complicated by FGR remain undetected and this translates to over an 8-fold increased risk of stillbirth when compared to normal controls (19.8 vs. 2.4/1000) [8]. In particular an estimated fetal weight (EFW) <3rd centile is most consistently associated with an adverse outcome [9].

Preeclampsia has traditionally been regarded as a condition of hypoperfusion with increased total peripheral resistance (TPR) resulting in hypertension. An elevated cardiac output (CO) is associated with the development of preeclampsia with changes apparent as early as the first trimester [10,11]. CO, stroke volume (SV), maternal heart rate (HR), TPR and end-diastolic volume have demonstrated potential in predicting FGR prior to its clinical manifestation [12,13].

Accurate monitoring of haemodynamic profiles has traditionally been performed using invasive methods such as pulmonary artery catheterization (PAC) [14,15]. Measurement of CO via PAC has been the clinical gold standard for central haemodynamic monitoring and is the reference standard used to compare non-invasive technologies [16–18]. However, it has been shown to have disadvantages and associated complications [19]. Non-invasive monitoring of haemodynamics has the advantages of being easy-to-use, safe and cost effective [20–24]. Transthoracic echocardiography (TTE) has been used in studies evaluating CO in pregnancy [10,25–27]. However, TTE is technically demanding, time-consuming, requires a skilled operator, and provides discrete intermittent data. Accuracy also depends upon image quality during acquisition [19].

Transthoracic bioreactance is a new technique of non-invasive continuous CO monitoring based on analysis of relative phase shifts of oscillating currents occurring when a current traverses the thoracic cavity [21]. Non invasive cardiac output monitor (NICOM®) observes the extent of time delay or phase shift which occurred and determines how much blood would have had to exit the left ventricle and enter the base of the aorta to cause the specific time delay thus calculating the stroke volume (SV). The ECG element of the NICOM® sensors detects heart rate (HR) and allows calculation of CO from Starling’s law (CO=HR×SV). Measurements derived from bioreactance based non-invasive CO assessment have been demonstrated by the HANDLE group and others to correlate well with results derived from TTE in the obstetric population [28,29].

A pilot study by Doherty et al. utilized NICOM to demonstrate the presence of differing haemodynamic profiles among women at high risk of uteroplacental disease [30]. The goals of this single centre prospective observational study were to demonstrate the altered haemodynamic profile in the presence of uteroplacental disease via NICOM® in low risk nulliparous women. In addition, we aimed to demonstrate the ability of altered haemodynamics to predict the development of PE, FGR or Gestational hypertension (GH) prior to the clinical presentation of disease.

### Study design

The HANDLE study (HAEMODYNAMIC Assessment in pregnancy and neonatal Echocardiography assessment) is a single centre prospective observational study conducted in a large tertiary maternity center in Ireland with an annual birth rate of approximately 8500. Eligible consecutive patients were
approached and enrolled between May 2014 and January 2016 to undergo serial assessment of maternal haemodynamics using the NICOM® (Cheetah Medical, Maidenhead, Berkshire, United Kingdom). Inclusion criteria were nulliparous patients >18 years old with a singleton non-anomalous pregnancy, normotensive and with no medical co-morbidities at their first prenatal visit. Ethical approval was granted by the Rotunda Research and Ethics Committee and written informed consent was obtained from all participants.

NICOM® assessments were performed at (14–16 weeks’, 18–22 weeks’, 26–30 weeks’ and review at least six weeks’ postpartum).

Haemodynamic monitoring was performed with the patient lying semi-recumbent, left lateral position to avoid aorto-caval compression. The NICOM® system was allowed to calibrate and each assessment was performed over 15 min with outputs recorded at one minute intervals. Data was obtained on CO, indexed CO (adjusted for maternal body surface area; COi), TPR, indexed TPR (adjusted for maternal body surface area; TPRi), SV, indexed SV (adjusted for maternal body surface area; SVi), systolic blood pressure (SBP) and diastolic blood pressure (DBP). Maternal characteristics, pregnancy outcome data, delivery details and neonatal outcomes were recorded.

**Fig. 1.** The reported nulliparous PE rate in the Rotunda hospital between 2004–2015. There was a significant fall in mean preeclampsia rates p < 0.001 pre and post 2005.

<table>
<thead>
<tr>
<th>Cardiac Variable</th>
<th>14 weeks</th>
<th>20 weeks</th>
<th>28 weeks</th>
<th>Postnatal</th>
<th>ANOVA p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NORMAL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CO (L/min)</td>
<td>6.3 (1.3)</td>
<td>6.4 (1.3)</td>
<td>6.6 (1.4)</td>
<td>5.6 (1.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SV (mL)</td>
<td>75 (17)</td>
<td>72 (17)</td>
<td>71 (15)</td>
<td>69 (16)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TPR (dynes/sec)</td>
<td>1180 (272)</td>
<td>1131 (258)</td>
<td>1102 (237)</td>
<td>1350 (301)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HR</td>
<td>85 (10)</td>
<td>90 (11)</td>
<td>95 (11)</td>
<td>83 (10)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>PE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CO/L/min</td>
<td>5.7 (10)</td>
<td>6.3 (0.8)</td>
<td>6.4 (1.5)</td>
<td>5.7 (1.2)</td>
<td>0.62</td>
</tr>
<tr>
<td>SV (mL)</td>
<td>72 (20)</td>
<td>77 (9)</td>
<td>71 (12)</td>
<td>71 (20)</td>
<td>0.92</td>
</tr>
<tr>
<td>TPR (dynes/sec)</td>
<td>1302 (305)</td>
<td>1181 (194)</td>
<td>1309 (542)</td>
<td>1421 (327)</td>
<td>0.76</td>
</tr>
<tr>
<td>HR</td>
<td>83 (10)</td>
<td>83 (9)</td>
<td>91 (14)</td>
<td>81 (8)</td>
<td>0.15</td>
</tr>
<tr>
<td><strong>GH</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CO (L/min)</td>
<td>6.2 (1.3)</td>
<td>6.5 (0.8)</td>
<td>6.6 (1.2)</td>
<td>6.1 (1.3)</td>
<td>0.39</td>
</tr>
<tr>
<td>SV (mL)</td>
<td>73 (18)</td>
<td>71 (11)</td>
<td>66 (16)</td>
<td>71 (21)</td>
<td>0.2</td>
</tr>
<tr>
<td>TPR (dynes/sec)</td>
<td>1262 (204)</td>
<td>1217 (204)</td>
<td>1243 (217)</td>
<td>1454 (396)</td>
<td>0.02</td>
</tr>
<tr>
<td>HR</td>
<td>87 (12)</td>
<td>92 (10)</td>
<td>101 (11)</td>
<td>87 (10)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>FGR</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CO (L/min)</td>
<td>5.8 (1.1)</td>
<td>5.9 (1.1)</td>
<td>6.0 (1.4)</td>
<td>5.6 (1.3)</td>
<td>0.48</td>
</tr>
<tr>
<td>SV (mL)</td>
<td>72 (17)</td>
<td>69 (15)</td>
<td>65 (18)</td>
<td>69 (18)</td>
<td>0.27</td>
</tr>
<tr>
<td>TPR (dynes/sec)</td>
<td>1209 (284)</td>
<td>1183 (300)</td>
<td>1208 (291)</td>
<td>1350 (393)</td>
<td>0.06</td>
</tr>
<tr>
<td>HR</td>
<td>83 (10)</td>
<td>87 (10)</td>
<td>94 (11)</td>
<td>83 (11)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Abbreviations: CO – cardiac output, TPR- total peripheral resistance, SV- stroke volume, HR- heart rate. Values are presented as means (Standard deviations). One way ANOVA with repeated measures was used to assess change over time.

1 Indicates p values < 0.05 compared with baseline assessment at 14 weeks (Bonferroni adjustment).

1 p value < 0.05 compared with respective Normal cohort value.
The cohort was divided into four groups based on their final clinical diagnosis of (1) PE, (2) GH, (3) FGR, and (4) uncomplicated pregnancies. The American College of Obstetricians and Gynecologists (ACOG) and the International Society for the study of Hypertension in pregnancy (ISSHP) define PE as blood pressure of ≥140/90 mmHg that occurs after 20 weeks of gestation in a woman previously normotensive and proteinuria, defined as urinary excretion of ≥0.3 g protein in a 24-h urine specimen. An elevated BP measurement was based on at least two measurements, taken using the same arm, at least two hours apart [31,32]. Pregnancies with GH were defined similarly but in the absence of proteinuria or other signs of end organ damage. An infant was described as FGR if the mother was normotensive and the birthweight was <10th centile when plotted on the WHO gender specific Neonatal and Infant close monitoring charts [33].

The sample size was calculated using the smallest expected group of 5% PE in comparison to a 10% FGR, based on the assumption of a 200 dyn·s difference in total peripheral resistance (TPR) between PE cases (1500 dyn·s) and control cases (1100 dyn·s) as demonstrated in a previous study in a high-risk cohort for PE [30]. A 5% level of significance, 80% statistical power and a 5% prevalence of PE were assumed in this nulliparous population. The estimated PE rate in the Rotunda nulliparous population was 5% so we aimed to recruit 400 patients over a two-year period to obtain 20 patients with PE [10,34–36]. As the HANDLE study was observational and descriptive in nature, there were no pre-defined management or delivery criteria and all decisions were made by the lead clinician managing the case.

Continuous data were presented as means (standard deviation) or as medians [inter-quartile ranges] as appropriate. Categorical data were presented as absolute values and percentages. Four group comparisons were conducted using the one-way ANOVA or Kruskal-Wallis one-way analysis of variance as appropriate. Two group comparisons were conducted using the independent t-test or Mann-Whitney U test. Proportions were compared using the Chi square test (or Fisher's exact test where appropriate). Haemodynamic trends over time were displayed using line charts and via one-way ANOVA with repeated measures. A Receiver Operating Characteristic (ROC) analysis was performed to determine the ability of variables by 16 weeks gestation to predict the evolution of PE, GH and FGR. Linear, non-linear and interaction terms were assessed using the Akaike Information Criterion. SAS Version 9.3 was used for statistical analysis.
Results

During the study period 15298 women booked to the Rotunda hospital of whom 6324 (41.3%) were nulliparous. Of 422 low risk nulliparous women recruited to the study 19 were excluded from the analysis for the following reasons: two (0.4%) chromosomal abnormalities, eight (1.9%) miscarriages, two (0.4%) intrauterine deaths at 27 weeks’ gestation, three (0.7%) cases of multiple pregnancy, one (0.2%) recruited to another research study and three recruited to the study in error. In addition 19 (4.5%) women withdrew their consent and 18 (4.3%) delivered at an alternative obstetric unit. This resulted in 366 patients completing the study protocol. The mean (±SD) gestational age at time of enrolment was 13.2 (±5.1) weeks. The mean age of participants was 29.1 (±5.1) years Table 1 further details the maternal demographics and fetal characteristics of the cohort. Of the 366 patients recruited, there were six cases of PE (1.6%), 18 cases of GH (4.9%) and 24 cases of FGR (6.6%) and a resultant 318 unaffected controls (86.9%).

Eight of the infants diagnosed as FGR were suspected antenatally, none of whom had abnormal umbilical artery Doppler assessments. Of the 24 cases of FGR, eight were a gestation and gender corrected birthweight <3rd centile. Five of these infants went on to deliver at a gestational age of greater than 40 weeks. There were no differences between the haemodynamic profiles of women whose infants were growth restricted <10th centile and women whose infants were growth restricted <3rd centile (data not shown).

The declining rates of PE in our institution are further detailed in Fig. 1. Of the six cases of PE, two occurred prior to 34 weeks gestation. None of the women with pregnancies complicated by hypertension were in receipt of antihypertensive therapy at the time of final antenatal haemodynamic assessment.

The differing haemodynamic profiles across the four groups are detailed in Table 2 and Figs. 2–6. As expected pregnancies complicated by PE and GH (Figs. 2–4) trended a higher TPR but demonstrated differences in their overall profile with differing SV and HR (Fig. 5). PE was associated with a reduction in HR in comparison to GH. Whereas GH had a lower SV in comparison to PE but this did not reach a level of significance (Fig. 5). Women with FGR, in the absence of hypertension demonstrated a lower HR, CO and lower SV but an increase in TPR in comparison to unaffected controls but not to the same extent as in hypertensive disease (Fig. 6).

The best independent predictors for the evolution of uteroplacental disease at 14 weeks’ gestation were CO in the prediction of FGR (AUC = 0.61; p = 0.002), TPR in the prediction of GH (AUC = 0.63;
Discussion

In this study we demonstrate four different haemodynamic profiles among women with pregnancies complicated with PE, GH and FGR and unaffected controls. In addition we have demonstrated the potential to predict the evolution of these disease states by a NICOM® derived haemodynamic profile.

There have been many studies detailing the altered cardiovascular profile of pregnancy in the presence of co-existing uteroplacental disease [13,37–40]. The majority of these studies have employed TTE in evaluation of the cardiac profile in the presence of uteroplacental disease. Previous TTE studies described a unique haemodynamic profile in PE of a lower CO and increased TPR when compared to unaffected pregnant controls. Using the novel automated NICOM® device we have shown these altered profiles in the setting of PE and FGR. Using NICOM® we have demonstrated a higher TPR of 1302 dyn s in PE. Although this did not achieve statistical significance due to the lower than expected number of PE, this is consistent with findings by Vasapollo et al. but with the advantage of being apparent at an earlier gestation in the first trimester [41]. In addition we have demonstrated a new profile in the setting of GH with differences in the SV and HR between the two hypertensive states (Fig. 5).

In the setting of fetal growth restriction, a fourth haemodynamic profile of uteroplacental disease exists as affected pregnancies are found to have a CO lower than the hypertensive counterparts and a moderate elevation in TPR when compared to pregnant controls but not reaching that of the hypertensive groups (Fig. 6) [10,12,30,40–43]. A similar NICOM® derived haemodynamic profile described in the late third trimester by Guy et al. also demonstrated a relatively unchanged HR, lower CO, reduced SV and elevated TPR [44]. Our findings are in keeping with Mahendru et al. who have reported a significant association

p < 0.02] and SVI in the prediction of PE (AUC = 0.62; p < 0.05). These are detailed further in Table 3. It was not possible to provide cut-offs for the univariate analysis secondary to the small numbers of disease states. The performance of haemodynamic variables was enhanced when combined in a multivariate logistic model as detailed in Table 4. TPR, CO and SV when combined with BP were significant predictors of pregnancies complicated by FGR (AUC = 0.64, p = 0.004; AUC = 0.65, p = 0.004; and AUC = 0.65, p = 0.007 respectively). Whereas in pregnancies complicated by PE, HR and SVI in combination with BP were also statistically significant predictors (AUC = 0.75, p = 0.017 and AUC = 0.77, p = 0.007 respectively). It was not possible to provide cut-offs for the multivariate analysis because of the nature of the inter-dependent relationship of the variables assessed.

Fig. 4. The differing haemodynamic profiles of gestational hypertension and unaffected pregnancy. Bars represent 1 standard error around the mean. Variables were compared by independent t-test and significant p-value of <0.05 are marked as *.
between pre-pregnancy to mid-pregnancy changes in CO and fetal weight gain [45].

Interrogation of maternal haemodynamics presents us with a novel and non-invasive opportunity to identify women at increased risk of uteroplacental disease. These differing maternal haemodynamic variables are evident prior to the clinical emergence of disease. The result of which would allow for better resource allocation by providing serial ultrasound biometry to women deemed high risk of FGR and ultimately improving the antenatal detection and management of FGR. Also the ability to differentiate GH from PE would allow for improved maternal risk stratification and improved prenatal care.

The strengths of the HANDLE study are its prospective nature and ability to plot the serial haemodynamic profiles of recruits across multiple time points amongst a low risk nulliparous population. Recruited pregnancies underwent serial monitoring including over 80% of women attending the postnatal element. The emergence of the novel bioreactance technology has the benefit of being easier to implement, as it is independent of both a skilled technician to perform and interpret the exam.

The study is limited by a lower than expected number of PE cases. This had a negative effect on the predictive performance of the haemodynamic variables and although differing from normal controls, we did not reach statistical significance. This was a reflection of overall falling PE rates within the hospital population at the time of the study (Fig. 1). As a result of the lower than expected AUC, an additional larger study would need to be undertaken before any recommendations with regards to a change in practice could be made. In addition these predictive capabilities should be reviewed in the context of improved risk stratification. However, this may not translate to improved perinatal outcomes in both the hypertensive and growth restricted cohorts.

The positive findings in this study substantiates the need for a larger multicentre prospective study interrogating the use of NICOM® derived maternal haemodynamics as a predictor of uteroplacental disease in comparison to current clinical practice. Additional longitudinal studies are also needed to interrogate the haemodynamic profiles of women prior to embarking on pregnancy to answer whether these observed aberrations are a direct result of placental mediated factors or a pre-determined risk prior to pregnancy.

Fig. 5. The differing haemodynamic profiles of preeclampsia and gestational hypertension. Bars represent 1 standard error around the mean. Variables were compared by independent t-test and significant p-value of <0.05 are marked as *.
Table 3
Assessment of independent haemodynamic variables in the prediction of uteroplacental disease.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Predictor</th>
<th>AUC</th>
<th>Odds ratio</th>
<th>OR95% CL</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FGR</td>
<td>CO</td>
<td>0.61</td>
<td>0.72</td>
<td>0.58–0.89</td>
<td>0.002</td>
</tr>
<tr>
<td>FGR</td>
<td>SV</td>
<td>0.58</td>
<td>0.98</td>
<td>0.96–0.996</td>
<td>0.02</td>
</tr>
<tr>
<td>GH</td>
<td>TPR</td>
<td>0.63</td>
<td>1</td>
<td>1.00–1.00</td>
<td>0.02</td>
</tr>
<tr>
<td>GH</td>
<td>HR</td>
<td>0.57</td>
<td>1.03</td>
<td>1.0–1.05</td>
<td>0.04</td>
</tr>
<tr>
<td>PE</td>
<td>SVi</td>
<td>0.62</td>
<td>1.1</td>
<td>1–1.1</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Abbreviations: AUC - Area under curve, OR- Odds ratio, CI- confidence limits, FGR- fetal growth restriction, GH- Gestational hypertension, PE- preeclampsia, CO- cardiac output, SV- stroke volume, HR- heart rate and, SVi- indexed stroke volume.

Table 4
The ability of haemodynamic variables (combined with BP and adjusted for gestational age) to predict the evolution of uteroplacental disease.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Predictor</th>
<th>AUC</th>
<th>Odds ratio</th>
<th>OR95% CL</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FGR</td>
<td>TPR</td>
<td>0.64</td>
<td>1</td>
<td>1–1.0</td>
<td>0.004</td>
</tr>
<tr>
<td>FGR</td>
<td>CO</td>
<td>0.65</td>
<td>0.73</td>
<td>0.59–0.91</td>
<td>0.004</td>
</tr>
<tr>
<td>FGR</td>
<td>SV</td>
<td>0.65</td>
<td>0.98</td>
<td>0.96–0.99</td>
<td>0.007</td>
</tr>
<tr>
<td>PE</td>
<td>SVi</td>
<td>0.77</td>
<td>1.1</td>
<td>1.0–1.1</td>
<td>0.007</td>
</tr>
<tr>
<td>PE</td>
<td>HR</td>
<td>0.75</td>
<td>0.94</td>
<td>0.9–0.99</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Abbreviations: AUC - Area under curve, OR- Odds ratio, CI- confidence limits, FGR- fetal growth restriction, PE- preeclampsia, TPR- total peripheral resistance, CO- cardiac output, SV- stroke volume, SVi- indexed stroke volume and HR- heart rate.

Acknowledgements

We would like to thank our patients, medical colleagues, midwifery staff and the hospital administrative staff who provided assistance that greatly assisted the research. The HANDLE Study was funded by the Health Research Board of Ireland and the Rotunda Foundation through the Medical Research Charities Group (MRCG) joint funding scheme (MRCG-2013-9).

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