MATERNAL CARDIOVASCULAR POTENTIAL AND KINETIC ENERGY INDICES IN PRE-ECLAMPTIC AND SMALL-FOR-GESTATIONAL AGE PREGNANCIES

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ABSTRACT

Introduction: Non-invasive assessment of maternal cardiovascular potential and kinetic energy can be used to derive the potential to kinetic energy ratio (PKR) and inotropy index (SMII). The balance of potential to kinetic cardiovascular energy is a measure of the balance between blood pressure and blood flow. The aim of this study is to evaluate PKR and SMII in pregnancies complicated by hypertensive disorders (HDP) and/or small-for-gestational age (SGA) birth.

Methods: This was a prospective study which enrolled women with singleton pregnancies between 10 to 41 weeks' gestation. Women with uncomplicated pregnancies and those who developed HDP and/or SGA were enrolled for cardiovascular profiling from 20 weeks' gestation. Measurements of the cardiovascular parameters were performed with a non-imaging ultrasound cardiac output monitor (USCOM-1A®, USCOM Ltd, NSW, Australia).

Results: A total of 683 women completed the study; 626 controls, 21 with HDP, 19 with SGA and 22 with HDP+SGA. PKR was significantly elevated in placental dysfunction compared to controls (HDP-alone 29.81±9.5, HDP+SGA 44.33±21.74, SGA-alone 31.05±13.14, Controls 22.30 ±7.93, all $p<0.05$). SMII values were only significantly lower in cases affected by SGA compared to controls (SGA 1.47 ±0.23 W/m^2 vs Controls 1.75 ±0.40 W/m^2, $p<0.005$). These differences remained statistically significant even when the analysis was undertaken using MoM values corrected for gestation.

Conclusions: The findings of this study suggest that point of care non-invasive cardiovascular profiling using PKR and SMII may help better delineate pregnancies affected by specific placental disorders versus those exhibiting health cardiovascular adaptation to pregnancy. Pregnancies affected by HDP and/or SGA appear to exhibit

distinctive profiles in PKR and SMII that reflect low kinetic energy with placental disorders, but high potential energy in pregnancies affected by HDP.

Contributions: PKR and SMII are novel indices that reflect both cardiovascular and placentation disorders of pregnancy. They reveal high PKR values in HDP and/or SGA due to higher PE. SMII is low in SGA-alone cases due to lower kinetic energy. However, SMII remains unchanged in hypertensive states. Furthermore, the non-invasive point of care demonstrates the physiological high-flow & low-resistance adaptation of pregnancy.

KEY WORDS: USCOM, SMII PKR, Pregnancy, Haemodynamics, Potential energy, Kinetic energy, hypertension, pre-eclampsia, fetal growth restriction

INTRODUCTION

The pathogenesis underpinning placental disorders is still not fully understood[1]. Historically, poor primary placental development has been suggested to be the physiopathology behind hypertensive disorders of pregnancy (HDP) and small for gestational age (SGA) birth. Although, poor placentation is implicated in early-onset or preterm placental disorders, there are some inconsistencies in the medical literature regarding the placental origins theory[2]. These inconsistencies are particularly apparent for late onset placental disorders which, in contrast, seem more likely to be produced by acquired placental dysfunction. The prevailing hypothesis is that the latter occurs secondary to maternal cardiovascular dysfunction in the face of increased pregnancy haemodynamic demands with advancing gestation[3–10]. Subsequent placental hypoperfusion leading to placental dysfunction may then manifest as hypertensive disorder of pregnancy (HDP) or small-for-gestational age (SGA) birth[11–13].

Some researchers have suggested that cardiovascular profiling might help with screening, diagnosis and management of placental disorders. Non-invasive continuous wave doppler cardiac output monitoring uses velocity-time integrals (VTIs) to derive several indices that reflect specific components of haemodynamic function such as stroke volume, cardiac output, and vascular resistance[14]. When the heart contracts, it transfers energy to the circulating blood. This energy may be divided in two types (1) Potential Energy (PE) such as with blood pressure and (2) Kinetic energy (KE) as for blood flow. The algorithm that integrates the maternal biometric profile and VTIs can also estimate cardiovascular potential and kinetic energy to derive potential

to kinetic energy ratio (PKR) and the inotropy index (SMII)[15]. The balance of potential to kinetic cardiovascular energy (PKR) is a measure of the balance between blood pressure and blood flow – possibly a better reflection of composite maternal myocardial performance than individual haemodynamic indices. The aim of this study is to evaluate the potential to kinetic energy and inotropy indices in pregnancies complicated by HDP and/or SGA birth.

METHODS

Patients

This was a prospective study which enrolled women with singleton pregnancies between 10 to 41 weeks' gestation attending a tertiary hospital in Southwest London between September 2012 and Jun 2017. To establish the reference range for potential and kinetic energy ratios, women without any pre-existing medical problems at the time of booking and who did not develop HDP, SGA or other complications in the pregnancy were recruited. Women who developed HDP and/or SGA were enrolled for cardiovascular profiling from 20 weeks' gestation. SGA was defined as a neonate having a birthweight below the 10th centile. Women with HDP were divided into two groups: those that had an SGA neonate (HDP+SGA) and those with an appropriately grown neonate (HDP-only). According to the modified ISSHP criteria, those in the HDP+SGA group had preeclampsia whilst those in the HDP-only group had either gestational hypertension or preeclampsia. Local research ethics committee approval (12/LO/0810) was obtained prior to data collection and informed written consent was obtained from all study participants. All women were examined by their midwives or obstetricians and both maternal and fetal wellbeing were confirmed prior to hemodynamic assessment, which was conducted only once per woman. Gestational age (GA) was calculated from crown–rump length measured at 11 to 13+6 week of gestation or from head circumference if the woman was more than 14 weeks at first scan.

Cardiovascular assessment

Measurements of the cardiovascular parameters from the aortic route were performed in standardised conditions as described in in detail previously[16,17]. In brief, women were positioned in a semi-recumbent position and a non-imaging probe was used in the suprasternal notch to obtain VTI to derive indices (USCOM-1A® - ultrasound cardiac output monitor, USCOM Ltd, NSW, Australia). Blood pressure was measured using Microlife® BP 3BTO-A (Microlife Corporation Microlife, Taipei, Taiwan).

Statistical analysis

Gestation dependent reference range models were fitted using a weighted cubic regression curve[18,19]. If normality of the residuals was not assumed, a $\log_{10}$ transformation was performed. The mean absolute residuals were then multiplied by $\sqrt{(\pi/2)}$ and modelled on GA using a weighted curved regression to obtain the Standard deviation (SD). The 95% reference interval was calculated as $\mathrm{mean(GA)} \pm \mathrm{Z} \times \mathrm{SD(GA)}$ where Z=1.959964. The 5th and 95th centile lines were plotted using Z =1.644854. The absolute mean residual (50th centile) was also use as a reference value to calculate the multiples of the median (MOM) in HDP and SGA pregnancies. Homogeneity of proportion between two or more populations was assessed by the chi-square test[20] (X^2). Categorical data were presented as number and percentage, while continuous data were presented as the median and interquartile range (IQR). Continuous data were examined using the Shapiro-Wilk test to assess the distribution of data. Chi-Square test, or Fisher's exact test when appropriate, was used to compare the categorical variables. Mann Whitney-U test was used to compare the medians of the hemodynamic variables between the two groups. A p-value less than 0.05 was deemed statistically significant. The statistical software used were MedCalc® V-

14.8.1(MedCalc Statistical Software, 2014) and SPSS (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp)

RESULTS

A total of 683 women completed the study; 626 controls, 21 with HDP, 19 with SGA and 22 with HDP+SGA. The controls were distributed across all gestations (130 in the 1st trimester, 96 in the 2nd trimester and 400 in the 3rd trimester). The reference ranges obtained from the controls for potential to kinetic energy ratio (PKR) and ionotropic index (SMII) are shown in Figures 1 and 2. The PKR remained between 20-30 throughout gestation with a slight increase towards term, whilst SMII was between 1.6-1.7 W/m^2 with a slight drop at late term.

The comparison of demographic variables and cardiovascular indices obtained from the pregnancies complicated by HDP with or without SGA against gestationally-matched healthy pregnant women is shown in Table 1. Statistical comparisons with the 82 gestation-matched controls are shown in Table 2 (Supplemental Tables 1 and 2) and with multiples of the median (MoM) corrected for gestational age in Figures 3 and 4.

The PKR was significantly elevated in placental dysfunction compared to controls (HDP-alone 29.81±9.5, HDP+SGA 44.33±21.74, SGA-alone 31.05±13.14, Controls 22.30 ±7.93, all $p<0.05$). These differences remained statistically significant even when the analysis was undertaken using MoM values corrected for gestation (Figure 3). SMII values were only significantly lower in cases affected by SGA compared to controls (SGA 1.47 ±0.23 W/m^2 vs Controls 1.75 ±0.40 W/m^2, $p<0.005$), and this finding persisted with MoM-based analysis.

DISCUSSION

Summary of main results

The findings of this study demonstrate stable maternal cardiovascular function with a stable ionotropy index (SMII) throughout normal pregnancy accompanied by a slight increase in potential to kinetic ratio (PKR) near term. HDP and/or SGA is universally associated with significantly reduced kinetic energy compared to controls. HDP with SGA is associated with a significant rise in PKR due to an increase in potential energy, whilst SGA demonstrates low SMII due to decreased kinetic energy.

Interpretation of study findings and comparison with published literature

The potential to kinetic energy ratio (PKR) reflects the balance in between blood pressure and blood flow. In healthy adults, the normal ratio is around 30 (30 to 1)[14], and it appears unchanged in pregnancy except for a slight rise near term. As PKR is a dimensionless ratio, like blood pressure, it does not need to be corrected for maternal characteristics such as height and weight. Similarly, the inotropic index (SMII), is the sum of the potential and kinetic energies produced by cardiac contraction (inotropy) - corrected by the body surface area (BSA) to make results comparable. The finding of low kinetic energy – equivalent to poor blood flow and impaired perfusion - in both HDP and SGA pregnancies is consistent with previous echocardiographic studies demonstrating impaired cardiovascular function in both disorders[4,5,7]. Within the pathological pregnancies (HDP±SGA), potential energy (and PKR) is higher in HDP and lower in SGA. Elevated PKR is consistent with a maternal low flow and high resistance state in these pathological pregnancies as typically occurs un hypertension.

Kinetic energy (and SMII) is lower in SGA pregnancies consistent with poorer cardiac contractility in SGA cases, which has been previously reported[21–23].Valensise *et al*.[21], reported lower contractility (SMII 1.40 *W/m*^{2}) was associated to lower birthweight babies – findings which were confirmed in two similar studies [22,23].

Clinical and research Implications

HDP and/or SGA present with characteristic patterns of PE, KE, PKR and SMII haemodynamic profiles which may be ascertained by a relatively cheap point-of-care instrument that requires very little training - unlike echocardiography. Assessment of PE and KE in at-risk pregnancies may be of clinical value in distinguishing pathological from normal pregnancies, as HDP pregnancies typically demonstrate high PKR and SGA pregnancies exhibit low SMII compared to controls. Prospective and blinded studies will be required to establish the clinical value of this point-of-care tool in effective medical triage and the impact on maternal and neonatal outcomes. The study findings also support the hypothesis that maternal cardiovascular impairment is a consistent finding in both HDP and SGA – traditionally considered to be 'placental' disorders. Normal pregnancy is associated with stable PKR and SMII haemodynamic indices throughout pregnancy, whereas HDP pregnancies are characterised by increased PKR/potential energy and SGA associated with reduced SMII/kinetic energy due to reduced cardiac contractility.

Strengths and limitations

The main strengths of our study are the prospective assessment of a large cohort of pregnancies with HDP and SGA as well as control pregnancies. Furthermore, in case

variables could be affected by gestational age, we used gestation matched controls and device-specific reference ranges. One limitation of the study is that as many cardiovascular indices, there is the potential for PKR and SMII to vary with body morphology, but the use of ratios should have minimised this effect. Furthermore, the indices studies are obtained from a peripheral waveform and the repeatability and reproducibility of these indices need to be established before screening studies are undertaken to establish their clinical utility.

CONCLUSIONS

The findings of this study suggest that point of care non-invasive cardiovascular profiling using PKR and SMII may be helpful in distinguishing pregnancies affected by specific placental disorders versus those exhibiting healthy cardiovascular adaptation to pregnancy. Pregnancies affected by HDP and/or SGA appear to exhibit distinctive profiles in PKR and SMII that reflect low kinetic energy with placental disorders, but high potential energy in pregnancies affected by HDP. These findings support the hypothesis of impaired maternal cardiovascular function in the pathogenesis of both HDP and SGA, but the sensitivity and specificity of PKR and SMII for these uteroplacental disorders still to be established.

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Table 1: Maternal characteristics and pregnancy outcome for the study population. Data provided as mean (standard deviation).

	Controls (n=82)	HDP-alone (n=21)	HDP and SGA (n=22)	SGA-alone (n=19)
Maternal characteristics				
Age (yrs)	32.37 (5.70)	31.75 (6.36)	31.93 (4.15)	31.58 (6.62)
Height (m)	1.63 (0.06)	1.62 (0.07)	1.60 (0.07)	1.60 (0.07)
Weight (Kg)	75.38 (2.63)	85.05 (15.47)	83.99 (14.62)	73.85 (14.02)
BMI (Kg/m^2)	28.02 (4.34)	32.42 (7.28)	32.72 (6.16)	28.79 (5.28)
BSA (m^2)	1.88 (0.18)	2.02 (0.21)	2.00 (0.22)	1.84 (0.20)
GA at measurement (wks)	27.21 (1.32)	26.27 (2.12)	26.27 (1.89)	27.03 (1.66)
Ethnicity				
Caucasian	61.0%	52.4%	36.3%	26.3%
Afro-Caribbean	18.3%	14.3%	31.8%	15.8%
Asian	17.1%	23.8%	27.3%	57.9%
Other	3.6%	9.5%	4.6%	0%
Pregnancy outcomes				
GA at birth (wks)	39.18 (4.51)	36.78 (5.42)	31.41 (5.39)	36.67 (4.17)
Birth weight (g)	3333.8 (684.1)	2644.2 (829.3)	1300.7 (764.1)	2195.7 (696.8)

Table 2: Maternal cardiovascular profiles in the various study groups. Data given as mean (SD). Symbols indicate statistical significance from: Control (†), HDP-alone (*), HDP+SGA (#) or SGA-alone ($)

	Control (n=82)	HDP alone (n=21)	HDP+SGA (n=22)	SGA alone (n=19)
Measured CV indices				
MAP (mmHg)	85.11 (7.64)$^{*\#}$	99.69 (13.85)$^{\dagger\#\$}$	111.28 (13.30) $^{\dagger*\$}$	87.12 (8.82)$^{*\#}$
HR (bpm)	82.84 (13.17)	82.20 (9.80)	80.12 (17.66)	85.21 (15.04)
SV (ml)	86.38 (16.96)$^{\#\$}$	83.65 (18.35)$^{\#}$	69.37 (19.36)†*	72.83 (15.42)†
Calculated CV indices				
SVI (ml)	46.20 (9.50)$^{\#\$}$	41.73 (9.72)$^{\#}$	34.97 (9.12)†*	39.62 (8.13)†
CO (L/min)	7.08 (1.50)$^{\#\$}$	6.81 (1.48)$^{\#}$	5.42 (1.10)†*	6.05 (0.94)†
CI (L/min/m^2)	3.78 (0.83)$^{\#\$}$	3.39 (0.73)$^{\#}$	2.74 (0.54)$^{\dagger*\$}$	3.29 (0.49)$^{\dagger\#}$
TPR (dyn·s/cm^5/m^2)	1012.64 (227.04)$^{*\#\$}$	1229.90 (295.44)$^{\dagger\#}$	1709.57 (520.71)$^{\dagger*\$}$	1187.15 (246.92)$^{\dagger\#}$
TPRI (dyn·s/cm^5/m^2)	1900.35 (443.08)$^{*\#\$}$	2476.80 (608.54)$^{\dagger\#}$	3360.76 (869.36)$^{\dagger*\$}$	2187.56 (515.29)$^{\dagger\#}$
Novel CV indices				
PE (mJ)	980.31 (215.27)$^{*\#\$}$	1104.70 (250.19)$^{\dagger\$}$	1086.87 (398.29)$^{\$}$	837.30 (151.25)$^{\dagger*\#}$
KE (mJ)	52.18 (30.17)$^{\#\$}$	43.10 (21.74)	36.82 (40.61)†	31.97 (15.63)†
PKR	22.30 (7.93)$^{*\#\$}$	29.81 (9.5)$^{\dagger\#}$	44.33 (24.27)†*	31.05 (13.14)†
SMII (W/m^2)	1.75 (0.40)$^{\$}$	1.77 (0.41)$^{\$}$	1.72 (0.48)$^{\$}$	1.47 (0.23)$^{\dagger*\#}$

Supplemental Table 1: Statistical comparisons of measured variables between various study groups * denotes statistical significance (P<0.05)

	HDP-alone vs Controls	HDP-SGA vs Controls	SGA-alone Vs Controls	HDP-Alone vs HDP-SGA	HDP-Alone Vs SGA-alone	HDP-SGA vs SGA-Alone
Measured CV indices						
MAP	**<0.001***	**<0.001***	0.319	**0.010***	**<0.001***	**<0.001***
HR	0.835	0.674	0.492	0.671	0.453	0.357
SV	0.519	**<0.001***	**0.001***	**0.030***	0.052	0.728
Calculated CV indices						
SVI	0.058	**<0.001***	**0.006***	**0.038***	0.465	0.143
CO	0.479	**<0.001***	**<0.001***	**0.002***	0.057	0.101
CI	0.050	**<0.001***	**0.001***	**0.004***	0.627	**0.003***
TPR	**<0.001***	**<0.001***	**0.003***	**<0.001***	0.624	**<0.001***
TPRI	**<0.001***	**<0.001***	**0.015***	**<0.001***	0.115	**<0.001***
Novel CV indices						
PE	**0.046***	0.095	**0.007***	0.806	**<0.001***	**0.014***
KE	0.188	**<0.001***	**0.002***	0.058	**0.022***	0.601
PKR	**0.003***	**<0.001***	**<0.001***	**0.016***	0.790	**0.010***
SMII	0.700	0.824	0.005*	0.725	**0.009***	**0.037***

Supplemental Table 2: Statistical comparisons of measured variables between groups Bonferroni corrected. * denotes statistical significance (P<0.05)

	HDP-alone vs Controls	HDP-SGA vs Controls	SGA-alone Vs Controls	HDP-Alone vs HDP-SGA	HDP-Alone Vs SGA-alone	HDP-SGA vs SGA-Alone
Measured CV indices						
MAP	**<0.001***	**<0.001***	1.000	**0.006***	**0.001***	**<0.001***
HR	1.000	1.000	1.000	1.000	1.000	1.000
SV	1.000	**<0.001***	**0.016***	**0.181***	0.312	1.000
Calculated CV indices						
SVI	0.348	**<0.001***	**0.036***	0.228	1.000	0.858
CO	1.000	**<0.001***	**0.026***	**0.012***	0.342	0.606
CI	0.301	**<0.001***	**0.006***	0.027	1.000	0.076
TPR	**0.020***	**<0.001***	0.096	**0.024***	1.000	**0.018***
TPRI	**0.001***	**0.001***	0.091	**0.001***	0.690	**0.001***
Novel CV indices						
PE	0.276	0.571	**0.042***	1.000	**0.001***	0.084
KE	1.000	**0.001***	**0.012***	0.348	0.132	1.000
PKR	**0.018***	**<0.001***	**0.001***	0.096	1.000	0.061
SMII	1.000	1.000	**0.015***	1.000	0.054	0.222

Figure 1: Scatterplot showing reference range for the potential to kinetic energy ratio (PKR) with gestational age in 626 women with an uncomplicated singleton pregnancy. Median (50th centile) shown as a solid line with 5th and 95th centiles shown as dotted lines.

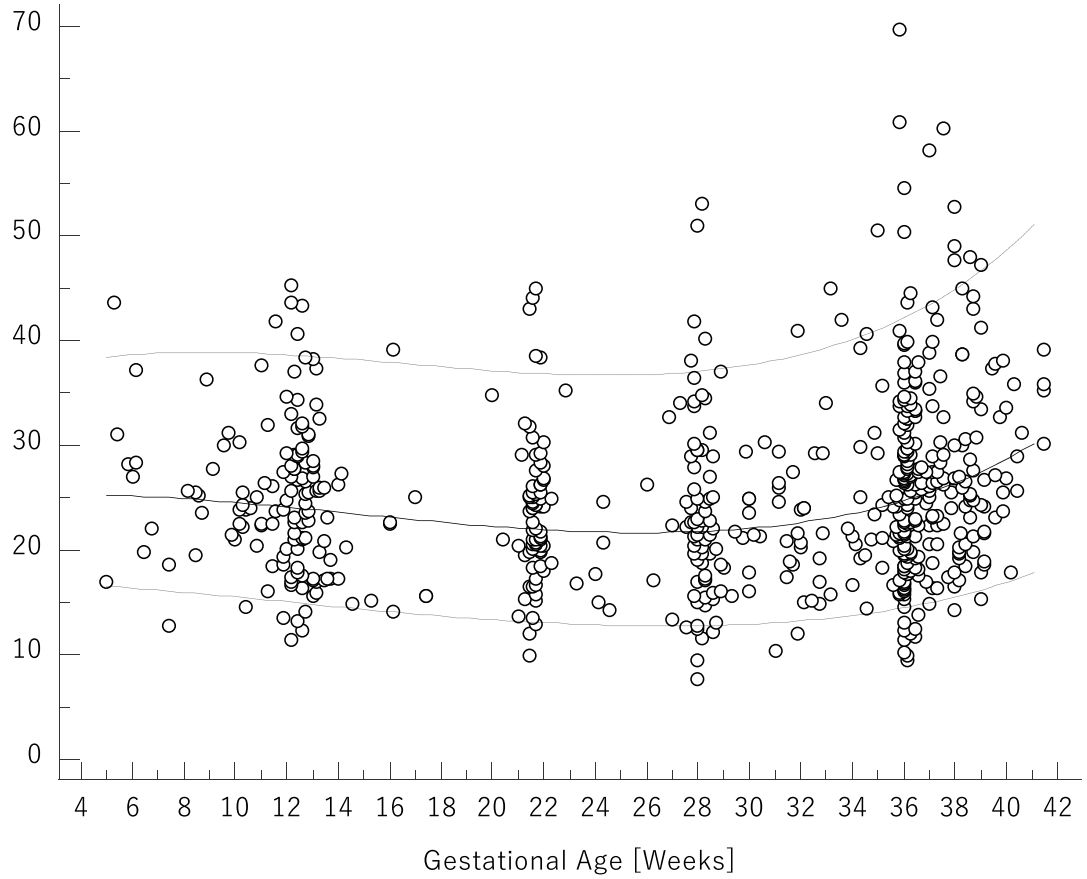

Figure 2: Scatterplot showing reference range for the inotropic Index (SMII) with gestational age in 626 women with an uncomplicated singleton pregnancy. Median (50th centile) shown as a solid line with 5th and 95th centiles shown as dotted lines.

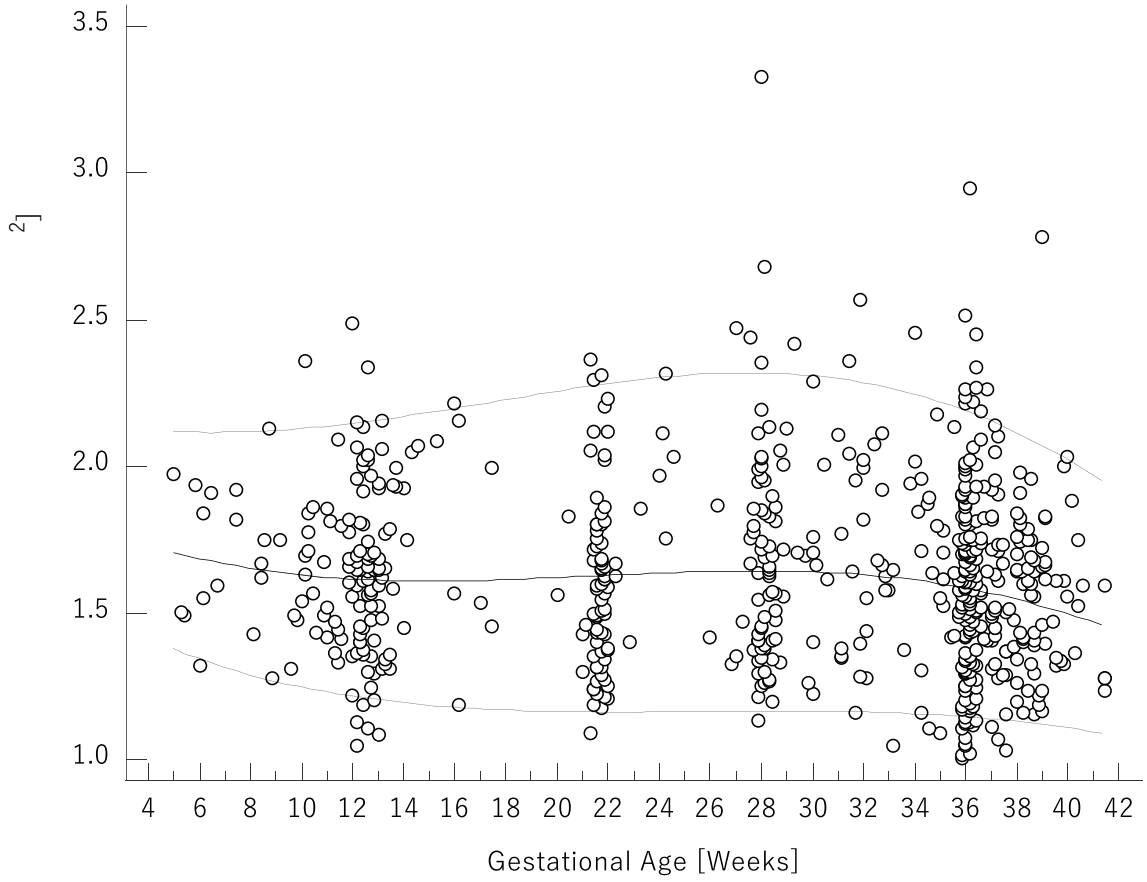

Figure 3: Box-plots showing the potential to kinetic energy ratio as multiples of the median (MoM) of the expected value for gestation in the three different phenotypes for uteroplacental dysfunction. Data shown as Median and interquartile range in the box.

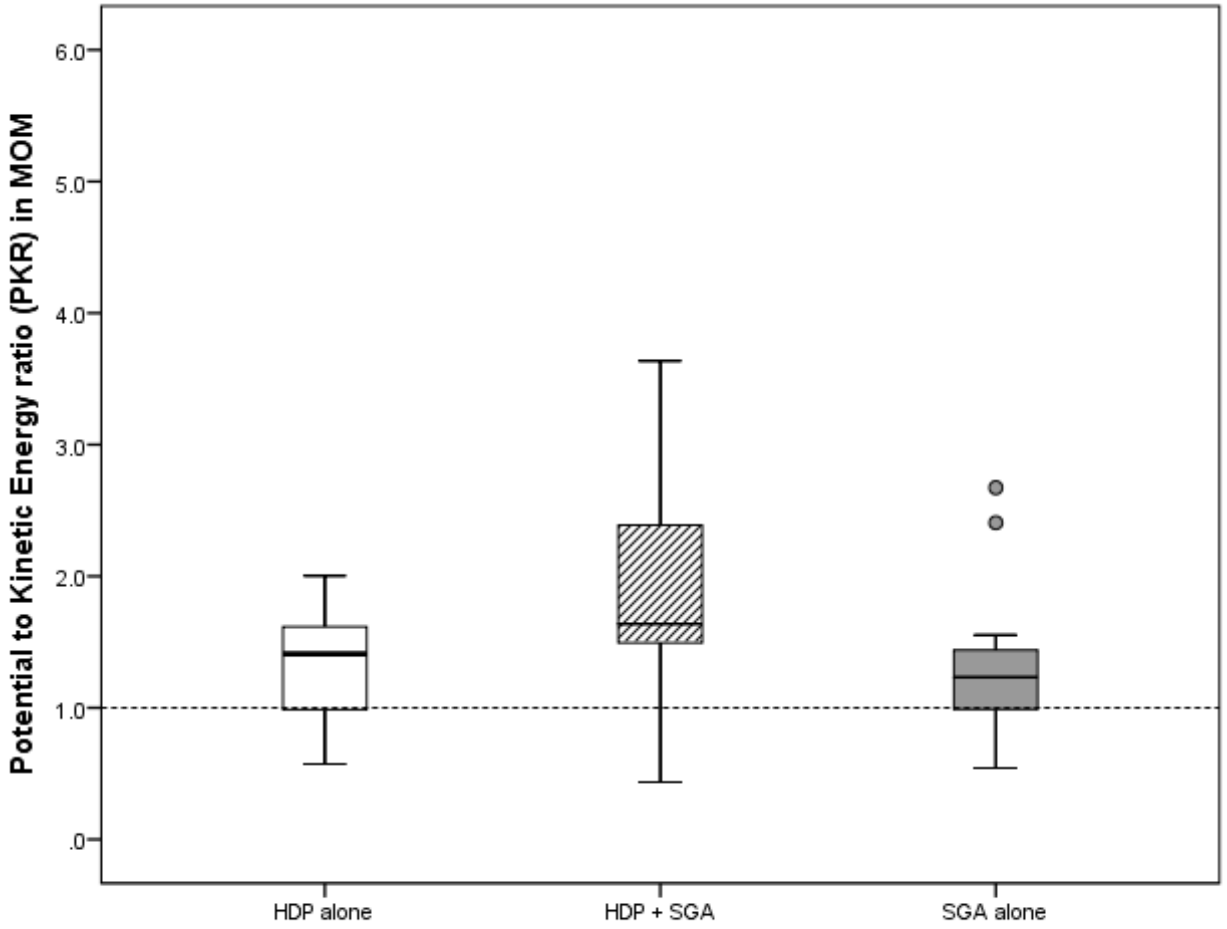

Figure 4: Box-plots showing the ionotropic index (SMII) as multiples of the median (MoM) of the expected value for gestation in the three different phenotypes for uteroplacental dysfunction. Data shown as Median and interquartile range in the box.