

The Changes of Aortic Stiffness During Normal Menstrual Cycle

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ABSTRAK

Kelajuan gelombang nadi (PWV), indeks augmentasi (AI) dan indeks kecergasan fotoplethimografi jari adalah petanda fungsi vaskular yang tidak invasif dan boleh meramal risiko penyakit kardiovaskular (CVD) pada masa depan. Dalam kalangan wanita, perubahan hormon estradiol dan progesteron semasa kitar haid dapat memberi kesan kepada fungsi vaskular. Oleh itu, kajian ini dilakukan untuk menyiasat variasi fungsi vaskular semasa fasa folikular dan luteal di kalangan wanita muda yang sihat. Seramai 22 orang wanita muda yang mempunyai kitar haid yang tetap telah terlibat. Tekanan darah (BP), indeks jisim tubuh (BMI), PWV, AI, PPGF, paras estradiol (Es) dan progesteron (Prog) telah diukur semasa fasa folikular (F) dan pertengahan luteal (L). Data dianalisis dengan menggunakan SPSS versi 20 dan aras $P < 0.05$ adalah dianggap signifikan. Purata umur subjek adalah 22.73 ± 0.60 tahun. Terdapat variasi yang signifikan pada hormon estradiol dan progesteron semasa kitaran haid iaitu paras estradiol ($EsF = 107.6 \pm 52.56$ pmol/L vs. $EsL = 555.16 \pm 152.79$ pmol/L, $P < 0.05$) dan progesteron ($ProgF = 0.62 \pm 0.26$ nmol/L vs. $ProgL = 46.74 \pm 14.59$ nmol/L, $P < 0.05$) adalah lebih tinggi semasa fasa pertengahan luteal berbanding fasa folikular. Paras PWV adalah lebih tinggi pada fasa folikular berbanding fasa pertengahan luteal ($PWVF = 6.67 \pm 0.66$ m/s vs. $PWVL = 6.31 \pm 0.52$ m/s, $P = 0.01$). Paras BP, BMI, PPGF ($PPGFF = 55.43 \pm 7.50\%$ vs. $PPGFL = 56.59 \pm 7.23\%$, $P = 0.41$) dan AI ($AIF = 12.87 \pm 5.13\%$ vs. $AIL = 10.80 \pm 4.52\%$, $P = 0.11$) tidak berubah antara kedua-dua fasa. Kesimpulannya, PWV berubah antara fasa folikular dan fasa pertengahan luteal semasa kitaran haid di kalangan wanita muda. Oleh itu, sejarah kitaran haid perlu diambil kira semasa pengukuran PWV di kalangan wanita.

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Kata kunci: fotoplethysmografi, kekenyalan arteri, kitaran haid

ABSTRACT

Pulse wave velocity (PWV), augmentation index (AI) and finger photoplethysmography fitness index (PPGF) are non-invasive markers of vascular function and may predict future cardiovascular disease (CVD) risk. In women, the changes from both oestrogen and progesterone levels during menstrual cycle may give significant impact on vascular function. Thus, this study was designed to investigate the variation of vascular function during follicular and luteal phase in healthy young women. Twenty-two healthy young women with regular menstrual cycle were recruited. Blood pressure (BP), body mass index (BMI), PWV, AI, PPGF, estradiol (Es) and progesterone (Prog) level were measured during follicular (F) and mid-luteal (L) phase. Data was analyzed via SPSS version 20 and P value < 0.05 was considered to be significant. The mean age of the subjects was 22.73 ± 0.60 years. There was significant variations of estradiol and progesterone levels during menstrual cycle whereby the level of estradiol (EsF = 107.6 ± 52.56 pmol/L vs. EsL = 555.16 ± 152.79 pmol/L, $P < 0.05$) and progesterone (ProgF = 0.62 ± 0.26 nmol/L vs. ProgL = 46.74 ± 14.59 nmol/L, $P < 0.05$) were higher in mid-luteal compared to follicular phase. PWV value was higher during follicular phase when compared to mid-luteal phase (PWVF = 6.67 ± 0.66 m/s vs. PWVL = 6.31 ± 0.52 m/s, $P = 0.01$). The levels of BP, BMI, PPGF (PPGFF = $55.43 \pm 7.50\%$ vs. PPGFL = $56.59 \pm 7.23\%$, $P = 0.41$) and AI (AIF = $12.87 \pm 5.13\%$ vs. AIL = $10.80 \pm 4.52\%$, $P = 0.11$) were unchanged between the two phases. In conclusion, PWV differs between follicular and mid-luteal phases of menstrual cycle in healthy young women. Thus, history of menstrual cycle must be taken into account when assessing PWV among women.

Keywords: arterial stiffness, menstrual cycle, photoplethysmography

INTRODUCTION

National Health and Morbidity Survey IV (Institute for Public Health 2011) in 2011 showed that heart disease accounted for 25.4% of the total mortality rate in Malaysia (Institute for Public Health 2011). In 2014, study conducted by World Health Organization (WHO) revealed that in Malaysia, the mortality rate for cardiovascular disease was about 36%

which is the major cause of mortality (World Health Organization 2014). It is very clear that non-communicable diseases such as cardiovascular disease contributes greatly to the mortality and disability that increased economic burden globally (Yusuf et al. 2001). From global burden of disease study which used disability-adjusted life year (DALY) as a standard unit in comparisons stated that non-communicable diseases contribute to

40.9% in global mortality among which 9.7% are attributable to cardiovascular conditions (Murray & Lopez 1997).

'Prevention is better than cure' – is one of the main approaches that would be the most appropriate model to deal with this serious health problem. Several researches were conducted to strengthen the screening for cardiovascular disease during early phase by assessing the vascular functions. Vascular functions can be assessed non-invasively by measuring the pulse wave velocity (PWV), augmentation index (AI) and finger photoplethysmography fitness index (PPGF). In Malaysia, PWV, AI and PPGF were found to be increased among those with risk factors and can be used as a screening for early vascular damage due to CVD risk factors (Aminuddin et al. 2013; Aminuddin et al. 2014; Aminuddin et al. 2016, Chellappan 2009).

Pulse wave velocity (PWV) reflects the velocity of the pressure wave that travels along the artery. Increased PWV is associated with increased aortic stiffness and so far, PWV along the aorto-iliac pathway has been accepted as the gold standard measurement of aortic stiffness (Laurent et al. 2007). PWV also demonstrates the predictive value for CV event (Mitchell et al. 2010). It may help in evaluation of individual risk of CVD (Shokawa et al. 2005).

Augmentation index is derived from the aortic pressure waveform (Wilkinson et al. 2000). It reflects the amount of pressure that augments the aortic pressure and it is mainly due to wave reflection (Kelly et al. 2001).

Higher value of AI indicates early return of reflected waves, which suggest increased arterial stiffness. Lower value of AI indicates good elasticity of the arterial wall (Wilkinson et al. 2000). Besides arterial stiffness, other factors that influence AI are total peripheral resistance, heart rate and body height (Laurent et al. 2007). Increased AI was found to be associated with increased risk of future CVD (Manisty et al. 2010). Finger photoplethysmography (PPG) is a technique to detect blood volume changes in a finger brought on by contraction and relaxation of the heart, by using an optical method (Challoner 1979). The use of PPG as measurement for vascular function is gaining popularity as it is user-friendly, non-invasive, valid and reliable. Several parameters that have been derived from PPG waveform analysis are stiffness index, reflection index and secondary derivative of PPG (Millasseau et al. 2002; Takazawa et al. 1998). PPG may be used for early screening of atherosclerotic disease (Elgendi 2012). Recently, PPGF was introduced. The unit of PPGF is in percentage with higher value reflects better vascular health status (Chellappan et al. 2008; Chellappan 2009). Recent study found that PPGF was associated with PWV and it was suggested that PPGF to be used as marker of aortic stiffness (Aminuddin et al. 2016).

In women, there is variation of hormonal level during menstrual cycle. In a normal cycle, oestrogen and progesterone levels are increased during luteal phase and are decreased during follicular phase (Ounis-Skali et al. 2006). Oestrogen modulates

vascular function by increasing nitric oxide (NO) level in the blood and this may lead to reduce aortic stiffness (Hayashi et al. 1995; Rajkumar et al. 1997). Previous studies found that vascular functions changed during menstrual cycle (Robb et al. 2009; Madhura & Sandhya 2014; Hayashi et al. 2006) while other studies found no change (Ounis-Skali et al. 2006; Papaioannou et al. 2009).

Since vascular markers are good predictors of future CVD, their measurement must be valid, follow the protocol and should be standardized between laboratory. In this research, we focussed on premenopausal healthy women, where variation in menstrual hormones level may give an impact to the measurement of vascular functions. The measurement was done during follicular and luteal phase since the level of oestrogen and progesterone were markedly different between both phases. Previous studies that have been conducted were based on small sample sizes. The present study was conducted with the use of a larger and proper sample size. The significance of this study is that it may provide reliable information about the effects of menstrual hormones fluctuation in accessing vascular functions. Such information is needed in standardizing the guidelines to minimize the laboratory variability when performing vascular tests in women.

MATERIALS AND METHODS

This cross-sectional study was approved by the Universiti Kebangsaan Malaysia Medical Centre (UKMMC)

Ethics Committee (FF-2016-233). The recruitment of subjects was done from June 2016 until August 2016. Subjects were recruited among the female students who volunteered to participate in the study. The main study was conducted at Physiology Department, UKMMC. All the subjects were required to sign an informed consent form prior to participating in this study. The total sample size was 22. This was based on PWV parameter which needs the highest number of subjects. It was calculated by using PS sample size calculator with reference from previous study ($\alpha = 0.05$, power = 80%, mean difference = 2.5) (Blacher et al. 1999). The inclusion criteria were healthy young women, aged 20-40 years, with normal and regular menstrual cycle. The average menstrual cycle duration was 28 days with range of 25-35 days. The exclusion criteria were those with irregular menstruation, smoking, on hormone replacement therapy and supplement, pregnant lady, lactating women and those with chronic illness such as hypertension and diabetes mellitus. Hypertension was defined as persistent elevation of systolic blood pressure (BP) of 140 mmHg or greater and/or diastolic BP of 90 mmHg or greater or on antihypertensive (Chobanian et al. 2003) and diabetes mellitus was defined as fasting venous plasma glucose level more than 7.0 mmol/L (Alberti & Zimmet 1998).

Subjects were required to track and document their menstrual phases for the past three months to make sure they had regular menstrual cycle. The subjects were studied once during

follicular phase (day 2-5) and once during mid luteal phase (day 18-24) of one full menstrual cycle. During follicular phase (day 2-5), it is expected that the hormones level is low when compared to mid luteal phase (day 18-24), in which any change on vascular functions can be assessed.

MEASUREMENT OF PARAMETERS

1) Body anthropometry

Weight was measured by using digital scale (SECA, Hamburg, Germany) and height was measured without shoes by using a wall-mounted stadiometer (SECA, Hamburg, Germany). Body mass index (BMI) was calculated as weight in kilograms/height in meter square (kg/m^2).

2) Blood parameters

Venous blood sample was withdrawn after fasting for at least 6 hours and was collected in plain ethylenediaminetetraacetic acid (EDTA) tubes. Blood for measurement of hormone level was taken during follicular (F) phase and mid luteal (L) phase. Blood samples were sent to Pathology Lab of UKMMC for measurement of lipid profiles [serum triglycerides (TG), high density lipoprotein (HDL), low density lipoprotein (LDL) and total cholesterol (TC)], blood glucose and hormone levels (oestradiol and progesterone).

3) Resting blood pressure (BP), aortic BP and total peripheral resistance (TPR).

Blood pressure was measured in supine position after 5 mins rest (Vicorder, SMT Medical, Wuerzburg, Germany). A BP cuff was fixed on the subjects' right arm and was inflated for measurement of brachial BP via oscillometric method. At the same time, the brachial artery pressure waveforms were recorded. These pressure waveforms were transformed to aortic pressure waveforms by using a brachial-to-aortic generalized transfer function (GTF) and calibrated to brachial mean BP and diastolic BP for the estimation of aortic systolic BP (SBP), diastolic BP (DBP) and pulse pressure (PP).

Total peripheral resistance (TPR) is measured based on a proprietary algorithm, whereby TPR is derived from the drop of the aortic pressure wave. While a slow drop is associated with a high resistance, a fast drop is associated with a low resistance.

4) Pulse wave velocity (PWV) and augmentation index (AI)

The Vicorder (SMT Medical, Wuerzburg, Germany) was used to measure both parameters in supine position. For AI, the estimated aortic pressure waveform was used and AI was calculated as augmentation pressure/pulse pressure (PP) x 100 by inbuilt algorithm.

For measurement of PWV, a thigh cuff was placed on the right thigh to detect femoral artery pulsation and a neck cuff was placed around the neck to detect carotid artery pulsation. Length (L) between sternal notch and midthigh cuff was measured in

meter by using measuring tape. Both cuffs were then inflated to 65 mmHg simultaneously for 30 seconds using volume displacement method to get the corresponding oscillometric signals. The delays between the two recorded pulses (transit time) were determined by the software. Pulse wave velocity was calculated as length/transit time (m/s).

5) Finger photoplethysmography fitness index (PPGF)

The measurement was done in a room with controlled temperature between 20°C to 25°C. Subject was required to fast for at least 6 hours before the procedure. Prior to the measurement, subject was asked to take a rest in supine position for five minutes. PPG probe was then attached to index finger and measurement was done for 120 seconds. The details of PPGF measurement was published before (Aminuddin et al. 2016).

STATISTICAL ANALYSIS

The data were analyzed by using the Statistical Package for Social Sciences Version 20 (SPSS Inc., Chicago, IL, USA). The normality of data was determined by using Shapiro wilk test. All the data were normally distributed and presented in mean±standard deviation. The paired sample t-test was used to assess the significance of mean differences between the two phases. Differences were considered significant at a P value of less than 0.05.

RESULTS

A total of twenty-two (n=22) subjects were recruited with an average menstrual cycle length of 28±7 days. They were young females and the biophysical characteristics and their blood parameters are shown in Table 1. All the blood parameters were within the normal range.

The menstrual hormones are shown in Table 2. There were significant variations of oestradiol (Es) and progesterone (Prog) levels during menstrual cycle whereby the level of oestradiol and progesterone were lower in follicular (F) compared to midluteal (L) phase (EsF = 107.6 ± 52.56 pmol/L vs. EsL = 555.16 ± 152.79 pmol/L, P < 0.05) (ProgF = 0.62 ± 0.26 nmol/L vs. ProgL = 46.74 ± 14.59 nmol/L, P < 0.05).

The cardiovascular parameters and vascular functions are shown in Table 3. There were no significant changes for all the blood pressure components between follicular and luteal phase. The PWV value was higher in follicular phase when compared to luteal phase (PWVF = 6.67 ± 0.66 m/s vs. PWVL = 6.31 ± 0.52 m/s, P = 0.01). PPGF and AI between the two phases were unchanged (PPGFF = 55.43 ± 7.50% vs. PPGFL = 56.59 ± 7.23%, P = 0.41) (AIF = 12.87 ± 5.13% vs. AIL = 10.80 ± 4.52%, P = 0.11).

DISCUSSION

The current study enabled us to explore the complex relationships between fluctuations of menstrual hormones and vascular functions at two distinct

Table 1: Biophysical characteristics of the subjects

Variables	Result
Age (year)	22.73±0.60
Weight (kg)	51.16±12.93
Height (cm)	156.88±7.22
BMI (kg/m ²)	21.52±3.32
LDL (mmol/L)	3.17±0.77
HDL (mmol/L)	1.48±0.28
TG (mmol/L)	0.81±0.28
TC (mmol/L)	4.92±0.64
FBS (mmol/L)	4.78±0.40

The value are mean±SD; BMI=body mass index; LDL=low density lipoprotein; HDL=high density lipoprotein; TG=triglyceride; TC=total cholesterol; FBS=fasting blood sugar.

phases throughout the menstrual cycle. The findings in this present study showed that PWV changed significantly between follicular and luteal phase which was synchronised with the fluctuations of oestrogen and progesterone level throughout the menstrual cycle. However, no changes were observed for AI and PPGF.

THE EFFECTS OF MENSTRUAL CYCLE ON AI

Our study demonstrated a slight but not significant reduction in the AI in luteal phase of menstrual cycle. Previous

Table 2: Menstrual cycle hormones

	FP	LP	P value
Oestradiol (pmol/L)	107.6± 52.56	555.16±152.79	<0.05 [#]
Progesterone (nmol/L)	0.62±0.26	46.74±14.59	<0.05 [#]

The value are mean±SD; FP=Follicular phase; LP=mid-luteal phase

[#] significant

Table 3: Cardiovascular parameters and vascular functions during follicular and luteal phase

	FP	LP	P value
SBP (mmHg)	111.20±9.90	109.36±8.69	0.29
DBP (mmHg)	64.96±9.67	62.48±5.86	0.19
AoSBP (mmHg)	103.84±8.97	100.76±7.74	0.09
AoDBP (mmHg)	63.43±7.72	62.48±5.86	0.63
PP (mmHg)	46.24±5.69	46.84±4.86	0.61
AoPP (mmHg)	38.80±4.81	38.52±4.56	0.80
AI (%)	12.87±5.13	10.80±4.52	0.11
HR (bpm)	72.30±8.77	74.28±7.87	0.15
MAP (mmHg)	84.42±7.32	83.12±6.99	0.27
TPR (PRU)	0.85±0.26	0.82±0.17	0.50
PWV (m/sec)	6.67± 0.66	6.31± 0.52	0.01 [#]
PPGF (%)	55.43±7.50	56.59±7.23	0.41

The value are mean±SD; FP=follicular phase; LP=mid-luteal phase; SBP=systolic blood pressure; DBP=diastolic blood pressure; AoSBP=aortic systolic blood pressure; AoDBP= aortic diastolic blood pressure; PP=pulse pressure; AoPP=aortic pulse pressure; AI=augmentation index; HR=heart rate; MAP=mean arterial pressure; TPR=total peripheral resistance; PWV=pulse wave velocity; PPGF=finger photoplethysmography fitness index.

[#] significant

studies had supported our findings that no change occurs in AI in luteal phase when compared to follicular phase (Ounis-Skali et al. 2006). The results are also in accordance with a study by Papaioannou et al. (2009) whereby AI did not vary significantly throughout menstrual cycle.

Several factors that affect AI include PWV, heart rate, height and total peripheral resistance (TPR). There is decreased PWV and TPR may decrease AI (Kelly et al. 2001). Since PWV reduced during luteal phase in this study, it is expected that AI is also reduced. In addition, increased oestrogen may cause peripheral artery vasodilation and reduce the TPR, which may cause lower AI (Hayashi et al. 1995). Oestrogen has been demonstrated to increase production of both nitric oxide (NO) and prostacyclin by upregulating endothelial nitric oxide synthase (eNOS) activity and prostacyclin synthase via a receptor-mediated system in which it promotes vasodilation (Hayashi et al. 1995; Massion & Balligand 2003; Lekontseva et al. 2011). Further study has reported that the physiological changes observed during the luteal phase of menstrual cycle does cause a marked decrease in TPR and a significant decrease in mean arterial pressure in the mid luteal phase corresponding to oestrogen level (Hassan et al. 1990). However, our findings showed that AI and TPR did not vary significantly throughout two phases of menstrual cycle. We hypothesized that the reduction in PWV may not be enough to reduce AI in the current study. The lack of AI variations between the two phases also

could be explained by the antagonizing effect on oestrogen perhaps mediated by progesterone. Progesterone, being a competitive inhibitor of aldosterone at the mineralocorticoid receptors are thought to be responsible for the rise in RAAS hormones mainly angiotensin II and aldosterone during luteal phase (Quinkler & Diederich 2002; Komukai et al. 2010) which possessed vasoconstrictive effect that offsetting the vasodilator effect by oestrogen (Ounis-Skali et al. 2006). Other hormones such as follicle stimulating hormone (FSH), luteinizing hormone (LH), prolactin and antidiuretic hormone (ADH) were markedly fluctuating during luteal phase. These hormones cause vascular smooth muscle contraction in which responsible for arterial stiffness that counter balanced the vasodilator effect of oestrogen (Giannattasio & Mancia 2002). Minson et al. (2000) also stated that resting muscle sympathetic nervous activity and plasma noradrenaline concentrations were higher during mid luteal phase than in early follicular and no changed observed in transduction of sympathetic nerve activity into vascular resistance. The study suggested that oestrogen augmented baroreflex sensitivity of sympathetic outflow correspond to NO production in altering vascular resistance, however progesterone may have antagonized this effect.

Interestingly, one of the studies showed that the significant vascular endothelial modulation by oestrogen was actually dependent more on the number of vascular oestrogen receptors and NO production by

vascular endothelium in mouse aorta rather than oestrogen level (Rubanyi et al. 1997). In this study, the endogenous NO production was found to be independent on the circulating level of plasma 17 β -oestradiol. Therefore, it can be suggested that vascular diameter modulation perhaps dependent largely on number of vascular oestrogen receptors regardless of oestrogen level.

Several studies demonstrated that oestrogen and hormone replacement therapy in postmenopausal women caused a significant systemic vasodilatory effect and an improved in arterial compliance (Crook et al. 1991; Cacciatore et al. 1998; Higashi et al. 2001; Rajkumar et al. 1997). This may differ with our study that only represents the acute effect of oestrogen level variation on arterial wall properties and does not represent the chronic effect after a long-term exposure to hormone replacement therapy in postmenopausal women.

The current study was in contrast with study by Adkisson et al. (2010) which measured hormones at 4 time points: early follicular, late follicular, early luteal and late luteal. They revealed that AI reduced during late follicular and early luteal phase. Another study by Robb et al. (2009) also observed that AI reduced during luteal phase when compared to periovulatory phase. The possible discrepancy in our result and theirs was probably due to different phases of menstrual cycle used to assess menstrual hormonal fluctuation.

THE EFFECTS OF MENSTRUAL CYCLE ON PWV

Our study revealed a significant reduction in PWV during midluteal phase compared to follicular phase. Another study by Hayashi et al. (2006) found that central arterial compliance (carotid artery compliance) also varied during menstrual cycle. However, their study found that carotid arterial compliance increased during menstruation and decreased during early and late luteal phase. The difference in method, type of artery and time of hormonal measurement may account for this discrepancy.

The significant changes in PWV in this study is not well understood. A previous study showed that NO increased large artery distensibility (Wilkinson et al. 2002). In a sheep model, infusion of acetylcholine and glyceryl trinitrate reduced PWV of the common iliac artery. The author suggested that changes in smooth muscle tone may result in changes in vessel diameter, wall thickness or wall stiffness. Since oestrogen may induce NO formation as stated earlier, this may be the possible mechanism that involved.

Another reason is that, other than increasing age, increased blood pressure (BP) is another important determinant of PWV. Increased pressure causes the wall to be stiffer (Cecelja & Chowienzyk 2009). Thus the combination of small but non-significant decrease in blood pressure during mid luteal phase could have at least contributed to the drop of PWV in the current study.

Our study is in contrast with another study by Williams et al. (2001) which involved 15 healthy women.

Hormones were measured at four time points which were early follicular, late follicular, early luteal and late luteal and used the same carotid-femoral PWV method as the current study. They found that aortic stiffness did not vary significantly over the course of menstrual cycle. Another study from Ounis-Skali et al. (2006), which involved a comprehensive assessment of central and peripheral PWV, central waveform morphology, and central aortic pressure too showed no significant changes in BP and PWV throughout phases of the normal menstrual cycle. Study by Robb et al. (2009), which studied ten healthy nulliparous women with regular menses in the early and midfollicular, periovulatory, and luteal phases of a single menstrual cycle showed no change in PWV. Another study by Adkisson et al. (2010) which measured PWV at early follicular, late follicular, early luteal and late luteal phase also found no changes. Another recent study also found that there was no change for PWV when measured at early and late follicular phase (D'Urzo 2016). The studies mentioned above failed to show significant changes which could be due to their sample size were smaller (less than 15 in all studies) compared to the current study (n=22) or different time in hormonal measurement. A study by Hayashi et al. (2006), that involved 10 healthy young women using PWV as a measure of aortic stiffness showed that arterial elastic properties did not fluctuate significantly with the phases of the menstrual cycle. The methodological difference in which the region used

for assessment of vascular properties from their study is different from ours where femoral-posterior tibialis was used for measuring PWV (peripheral arterial stiffness) and this may result in the discrepancy of the outcome.

THE EFFECTS OF MENSTRUAL CYCLE ON PPGF

Our study found that PPGF did not vary significantly despite with significant changes of hormonal level throughout the menstrual cycle. In contrast, study by Madhura & Sandhya (2014) in which PPG waveform was used to measure reflection index (RI) and stiffness index (SI) showed significant variation throughout menstrual cycle.

Aminuddin et al. (2016) found that PPGF correlated independently with PWV, suggested that PWV is one of the determinants of PPGF, however, its correlation with PWV was weak ($r = -0.27$). This perhaps explained the insignificant variation of PPGF despite with significant changes of PWV between two phases of menstrual cycle in the current study.

The strength of this study is that we evaluated all subjects health status strictly based on clinical and laboratory investigation and confirmation. There are several limitations that were encountered. The data was collected at two time points only (early follicular and mid luteal phase) and the findings may differ according to the varying levels of oestradiol, progesterone seen throughout the menstrual cycle. Secondly, the current study did not include data on other hormonal level which could significantly affect

vascular stiffness such as RAAS hormones (aldosterone, angiotensin II), FSH, LH and prolactin which could provide more solid evidence to support our observations.

CONCLUSION

This current study evaluated the changes of PWV, AI and PPGF at two distinct points of time throughout the menstrual cycle. PWV differed significantly between the two phases of menstrual cycle while AI and PPGF remained unchanged despite significant fluctuations of menstrual hormones. The underlying hormonal phenomenon on vascular properties was not well established in this study. Nevertheless, the data indicates that it is essential to take into consideration of patient's menstrual cycle when assessing central arterial stiffness in premenopausal women.

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