OLDER AGE GROUP IN PREGNANCY IS ASSOCIATED WITH INCREASED ARTERIAL STIFFNESS

A A Salmi, BSc[1], A G Nor Aliza, M Med (O&G)[2], N M Nik Zaki, MMed (O&G)[2], A R Wong, MRCP (Paeds)[3], Aida H Rasool MBBS, PhD[1*]

[1]Pharmacology Vascular Laboratory, [2]Obstetric and Gynaecology & [3]Paediatrics Department, School of Medical Sciences, Universiti Sains Malaysia, Health Campus, Kota Bharu

SUMMARY
Arterial stiffness is an index of vascular health; normal pregnancy is associated with reduced arterial stiffness. This cross sectional study compared arterial stiffness in older (≥35 years) and the younger (≤34 years) age groups of pregnant women. Arterial stiffness was assessed non-invasively in 66 pregnant women between 23 – 32 weeks gestation (41 women ≤ 34 years, 25 women ≥ 35 years) using the parameters pulse wave analysis and pulse wave velocity. Blood pressure (BP), body mass index (BMI), serum total cholesterol (TC) and fasting blood glucose (FBS) were also recorded. Mean ages of the younger and older age groups were 27.6±0.62 and 39.3±0.58 years; no significant difference was seen between the groups in their BMI, TC, FBS, SBP, DBP and gestational age. The older age group of women have increased arterial stiffness (augmentation index 19.4±1.9% vs 13.2±1.6%, p=0.015) and aortic stiffness (pulse wave velocity 8.7±0.3 vs 7.7±0.2 m/s, p=0.004) compared to the younger women. Linear regression analysis showed a positive significant correlation between age and augmentation index (R=0.278, p=0.026), and pulse wave velocity (R=0.350, p=0.004). We conclude that older pregnant women has increased arterial stiffness compared to a younger age group of pregnant women suggesting that vascular changes due to ageing occurs in pregnancy despite cardiovascular adaptations occurring in pregnancy.

KEY WORDS:
arterial stiffness, age, pregnant women

INTRODUCTION
Arterial stiffness is an index of vascular health; it is an independent risk factor for cardiovascular events and mortality in hypertension[1], diabetes[2] and the general population[3]. Arterial stiffness can be assessed non-invasively using the principles of pulse wave analysis (PWA) and the parameter pulse wave velocity.

In pregnancy, numerous studies reported that women with pre-eclampsia have increased arterial stiffness (i.e. reduced arterial compliance) as shown by increased values of central augmentation pressure, augmentation index (AI) and pulse wave velocity compared to pregnant women without pre-eclampsia[4-8]. Even after pregnancy, women with history of early onset pre-eclampsia had significantly higher arterial stiffness compared to controls with a history of uncomplicated pregnancy. Recently, Khalil suggested that the use of arterial pulse wave analysis (PWA) has the potential to be used as a predictive test for subsequent development of pre-eclampsia[7]. For a false positive rate of 11%, augmentation index at first trimester between the 11th and 13th week of pregnancy predicted 79% of women who went on to develop pre-eclampsia and 88% of those who developed the more severe early onset pre-eclampsia.

In non-pregnancy, arterial stiffness increased with increasing age[9,10,11]. Pulse wave velocity in the aorta increased markedly with age; central augmentation index also progressively increases with age[10]. However, for these studies, considerable individual variability in arterial stiffness was noted, for example, physical activity improved arterial stiffness compared to those in the sedentary group.

There are so far no studies that determine the effect of pregnancy age on arterial stiffness. During pregnancy, women undergo major physical, metabolic, hormonal and cardiovascular changes. Cardiovascular adaptations occurring in pregnant women include peripheral arterial vasodilatation and a substantial increase in plasma volume and cardiac output. Pregnant women had been reported to have lower central blood pressure (systolic and diastolic) and marked decrease in vascular resistance thus reduced arterial stiffness as assessed with the parameter augmentation index, compared to non pregnant controls[12]. Arterial stiffness as assessed by AI decreased with gestation reaching their nadir at around mid pregnancy, and remain low until delivery in normal pregnancy[12,13]. Mersich *et al.*, also reported that during the course of a pregnancy, aortic PWV gradually decreased from first to third trimester; however, the PWV increased again during the post partum period; this is supported by Oyama-Kato[8,14].

Due to these cardiovascular adaptations, it is possible that effect of increasing age with arterial stiffness will be attenuated in pregnancy, due to the reduced blood pressure, vascular resistance and increased arterial compliance in the pregnancy state. Thus this study aims to compare arterial stiffness as assessed by pulse wave analysis and carotid femoral pulse wave velocity between a younger (<35yo) and older age (≥35 yo) group of pregnant women. In this article, the age of 35 is chosen as the cut-off value, as it is considered as an 'advanced maternal age', which is defined as an expectant mother who will be at least 35 years by the time she delivers[15,16].

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Corresponding Author: Aida Hanum Ghulam Rasool, School of Medical Sciences, Universiti Sains Malaysia, 16150 Kota Bharu, Malaysia Email: aida@kb.usm.my Tel: 09-7676123/6143 Fax: 09-7653370

MATERIALS AND METHODS

This cross sectional, prospective study involved 66 pregnant women between 23 – 32 weeks gestation. The conduct of the study has been approved by the Ethical Committee of Universiti Sains Malaysia; all subjects gave written informed consent to participate. These women were divided into two groups based on their age, the younger age group of pregnant women (< 35 years old) and the older age groups of pregnant women (≥ 35 years old).

All women were non smokers without previous history of cardiovascular diseases such as chronic hypertension, pregnancy induced hypertension and arrhythmia. Women with fasting blood glucose > 6 mmol/L, multiple pregnancies or have serious maternal illnesses such as cancer, liver and renal diseases were excluded. All women were not taking any vasoactive medications, steroids, and were not on any non-steroidal anti-inflammatory drugs at least two weeks prior to being recruited. Fasting blood samples were taken from these women for measurements of serum total cholesterol, blood count and fasting blood sugar.

Subjects attended a vascular study session to assess arterial stiffness in the mornings, fasted for at least 4 hours in a quite room at room temperature of 24-25°C. All women did not drink alcohol during pregnancy, refrained from caffeine from midnight, and high salted food for 24 hours before vascular study. The women lie on a bed, with their head supported by a pillow, in a 30% left lateral position to avoid vena cava compression by the uterus. A quite rest period of at least fifteen minutes was allowed for each patient for acclimatisation. Blood pressure was then taken using an automated blood pressure sphygmomanometer (Omron MX3, Japan) which was standardised for all patients.

Arterial stiffness was then assessed using the parameters aortic femoral pulse wave velocity (PWV) and percent augmentation index (AI%) obtained from pulse wave analysis as has been previously described (17,18). The Sphygmocor device (AtCor Medical Pty Ltd – Australia) was used to obtain these measures non-invasively.

Carotid femoral pulse wave velocity is a well established method to assess aortic stiffness. It gives the velocity of the pulse wave travel along the carotid-femoral segment by calculating the time delay between the pulse pressure waves at two different sites, a known distance apart. This is performed by placing and recording a pressure sensitive probe independently on the carotid followed by the femoral pulsations, and comparing the time delay at both sites against a simultaneously measured QRS complex (from the electrocardiography). The distance travelled by the pulse wave between the carotid and the femoral pulsations was measured externally. A higher PWV indicated increased aortic stiffness and vice versa. The repeatability of the measurement assessed by intraday and interday coefficient of variations for the investigator performing the measurement were 4.41% and 4.13% respectively.

Pulse wave analysis was used to assess systemic arterial compliance. The tip of the pressure sensitive tonometer (Millar for AtCor Medical – US) was gently compressed at the site of the radial artery to obtain the radial artery pressure waveform. A validated transfer function was used to derive the aortic pressure waveform from the radial waveform, enabling aortic pressures & certain central arterial indices to be measured including the parameter of interest, augmentation index. Augmentation index is the proportion of central arterial pressure that results from arterial wave reflection and is a commonly used measure of arterial stiffness[19]. A higher AI value indicates stiffer systemic arterial compliance and vice versa. The repeatability of the AI measurement assessed as intra and interday coefficient of variantions were 6.6% and 7.0% respectively. An average of two readings were recorded for the measurements of PWV and AI[17, 18] all measurements were taken by a single investigator throughout the study.

Statistical analysis was performed using the SPSS software version 12.0. Differences between groups in baseline characteristics and study parameters were evaluated using the independent t-test or Mann Whitney U test were applicable. If the set of data was normally distributed, the independent t-test was utilised; if the data was not normally distributed, then the Mann Whitnye U test was used. Both PWV and AI were normally distributed, as guided by descriptive methods such as data frequency histogram and the normal probablity plots. Thus paired t-test was used to determine difference between the two groups in these parameters. Linear regression analysis was used to compare relationship between two continuous variables. Data are given as mean ± standard error mean. Statistical significance was set at $p < 0.05$.

RESULTS

Sixty six women were studied, 41 were of the younger age group (below 35yo, mean age 27.6±0.6 years) and 25 patients were of the older age group (≥ 35yo, mean age 39.3±0.6 years). Demographic and laboratory characteristics of the subjects for both groups are presented in Table 1. The younger and older age groups of pregnant women did not differ in their mean gestational age, body mass index (BMI), systolic (SBP) and diastolic blood pressure (DBP) and laboratory measures.

Figure 1 shows pulse wave velocity values for the younger and older age group of pregnant women. The older pregnant women have significantly higher pulse wave velocity compared to the younger women (8.8±0.3 vs 7.7±0.2 m/s, p=0.004, paired t-test), indicating increased aortic stiffness in the older age group of pregnant women. Figure 2 shows augmentation index values for the two groups. Again, older age group of pregnant women have significantly higher AI values compared to the younger age group (19.3±1.9 vs 13.2±1.5%, p=0.015, paired t-test), indicating increased systemic arterial stiffness in the older age group of pregnant women.

Linear regression analysis performed to assess relationship between age and PWV showed a significant positive correlation between age and PWV (R value = 0.350, p = 0.004) where, as age increases, pulse wave velocity also increases indicating increased aortic stiffness. Linear regression analysis performed to assess relationship between age and augmentation index also showed significant positive correlation between age and augmentation index where, as age increases augmentation index values also increases indicating increased arterial stiffness (R value = 0.278, p = 0.026).

Table I: shows baseline characteristics and laboratory parameters for the older and younger age groups of pregnant women. Apart from age, there were no significant differences between the two groups. Values given as mean±sem.

Parameter (unit)	Older age group n=25	Younger age group n=41	P
Age (years)	39.31±0.58	27.57±0.62	0.015
Gestational age (weeks)	28.76±0.43	29.00±0.35	0.671
Fasting blood sugar (mmol/l)	4.21±0.14	4.08±0.10	0.460
Systolic blood pressure (mmHg)	109.4±2.48	107.5±1.83	0.523
Diastolic blood pressure (mmHg)	68.6±1.90	66.29±1.40	0.317
Total cholesterol (mmol/l)	6.24±0.18	5.82±0.16	0.093
Hematocrit (%)	34.08±0.57	34.98±0.49	0.246
Body mass index (kg/m²)	28.67±0.96	29.13±0.89	0.737

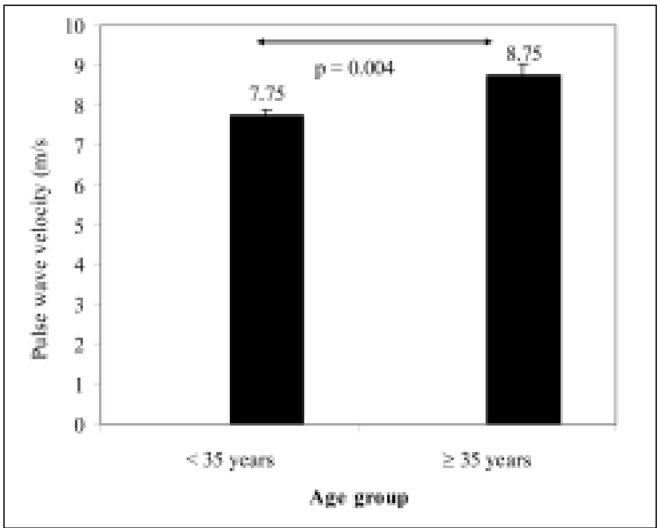

Fig. 1: shows pulse wave velocity values for the younger and older age group of pregnant women. Older women had significantly higher pulse wave velocity compared to the younger group of women (p=0.004)

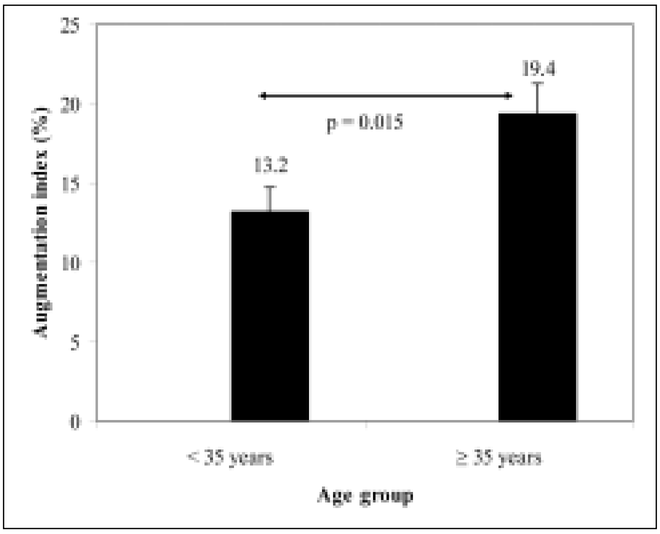

Fig. 2: Augmentation index values for younger and older age of pregnant women. Older women had significantly higher augmentation index values compared to younger pregnant women (p=0.015).

DISCUSSION

Our study showed that pregnant women in the older age group has increased arterial stiffness, as shown by increased augmentation index and aortic femoral pulse wave velocity values compared to their gestational age matched younger group. There was also positive correlation between age and augmentation index, and between age and pulse wave velocity among the pregnant women. This showed that, despite cardiovascular adaptations occurring in pregnancy which reduces peripheral vascular resistance and increased arterial compliance during pregnancy, the effect of age on arterial stiffness persists. The higher arterial stiffness in the older age group of pregnant women occurs despite no difference was seen between the two groups in their blood pressure. To our knowledge, this is the first study showing relationship between age and arterial stiffness in a pregnant population.

Increased arterial stiffness with age in non-pregnancy had been reported[9,10]. Age related changes in the vasculature are not only confined to large arteries, but also involve small arteries and arterioles. Structural and functional changes associated with aging may impair the compliance of the arterial circulation. In terms of vascular functional changes, altered regulation of vascular tone due to reduced presence or production of endothelium derived relaxing factors (EDRF) could increase arterial stiffness. Endothelial release of nitric oxide has been shown to be impaired with aging[20], atherosclerosis and diabetes. Reduced NO would not only produce vasoconstriction, which increases arterial stiffness, but would also promote vascular smooth muscle growth that could add a structural component to the increase in arterial stiffness.

Structurally, the thickening of the intima and media layers of the vascular wall play a role in the increased stiffness seen with ageing. The vascular media has been known to thicken and fibrose with age[21]. With advancing age, the distensibility of an artery decrease in proportion to the increase in collagen in the media, and to a lesser extent in the intima. Increased PWV has traditionally been linked to structural alterations in the vascular media including increased collagen, reduced elastin content, elastin fractures and calcification[22]. In large arteries, aging results in progressive deposition of calcium salts, fraying and fragmentation of elastin, and an increase in the number and cross linking of collagen fibers that alter the compliance characteristics of the vessel wall[23]. Intimal thickening could also contribute to arterial stiffness with aging; carotid intima media thickness increases 2-3 fold between 20 and 90 years of age.

Stiff arteries cause premature return of reflected waves in late systole, increase pressure load on ventricle, reducing ejection fraction, and increasing myocardial oxygen demand besides causing altered vascular wall properties. These result in higher systolic pressures with relative decrease in diastolic pressure, which could reduce coronary blood flow. In pregnant women, besides the above risk factors, other specific implications on the mother and fetus are currently not known. It is possible that the increased stiffness seen with ageing increased the risk of obstetric maternal complications such as pregnancy induced hypertension, gestational diabetes and placental abruption; these conditions more commonly occur in advanced maternal age [24,25]. It may also contribute to fetal risk such as fetal loss; stillbirth rates had been shown to rise with maternal age[26]. Women at advanced maternal age had been reported to havea higher risk for low birth weight and very low birth weight. Elvan Taspinar *et al.*, had reported that in normotensive pregnancy, there was a significant inverse relationship between birth weight centiles and PWV and pulse pressure. They have estimated that, an increase in 1 m/s in PWV is associated with a 17.6% decrease in birth weight centile, independent of BP. Taspinar *et al.* thus hypothesised that the higher arterial stiffness in pregnant mothers may contribute to inadequate plasma volume expansion that impedes optimal fetal growth causing reduced birth weight[27].

In non pregnancy, pulse pressure, PWV and AI are lower and baroreceptor reflex function is improved in older persons who are physically active compared to sedentary person[28], exercise also improves endothelial function in older persons[29]. However, the effect of increased physical activity on arterial stiffness in pregnancy is not known. Our oversight in not taking the physical activity history of these women may form a limitation of this study.

CONCLUSION

We conclude that, older age group of pregnant women has increased arterial stiffness compared to their gestational aged matched younger group of pregnant women. There was also a positive relationship between maternal age during pregnancy and arterial stiffness.

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