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Arterial stiffness in normal pregnancy as assessed by digital pulse wave analysis by photoplethysmography – A longitudinal study

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ABSTRACT

Introduction: It might in the future be valuable to screen for increased maternal arterial stiffness, i.e. low compliance, since it is associated with development of hypertensive complications in pregnancy. Digital pulse wave analysis (DPA) is an easy and manageable method for arterial stiffness assessment. We aimed to investigate gestational influence on DPA variables longitudinally, and establish gestational age-adjusted reference values in normal pregnancy.

Methods: DPA measurements were performed longitudinally up to five times during pregnancy in 139 healthy women. Reference curves for DPA variables aging index (AI), *b/a* and *d/a* relative to gestational age were calculated with linear and polynomial mixed-effects models, and the influences of age and parity investigated with analysis of variance and analysis of covariance. A $p < 0.05$ was regarded significant.

Results: All DPA variables were significantly associated with GA with best fit for a quadratic model. Arterial compliance peaked in the late second trimester. Age and parity independently influenced DPA variables but did not change the associations with gestational age.

Conclusions: DPA reflects longitudinal changes in arterial compliance in normal pregnancy but individual variance of DPA changes were greater than the influence of GA. Normal distributions of AI, *b/a* and *d/a* at 14–24 weeks are presented, but it remains to show whether these can be used to detect pathological hemodynamic alterations in pregnancy.

1. Introduction

Pregnancy is characterized by major maternal hemodynamic alterations. Heart rate (HR), stroke volume (SV), cardiac output (CO) and plasma volume increase in pregnancy as a response to a fall in systemic vascular tone [1,2] and total vascular resistance (TVR), accompanied by an increase in arterial compliance and decreased and delayed pulse wave (PW) reflection [2]. The cardiovascular adaption is initiated already in the first weeks of pregnancy [1,3], most likely due to a vasodilatory effect of estrogen [3–5]. Cardiovascular maladaptation is linked to subsequent hypertensive complications [6–8] and intrauterine growth restriction (IUGR) [9,10]. Thus, early screening for cardiovascular maladaptation may be of value for evaluating risk for adverse pregnancy outcome.

"Arterial stiffness", a term describing arterial elasticity, is determined by vascular tone, arterial wall properties and hemodynamic factors, and is an independent risk factor for cardiovascular morbidity and mortality [11,12]. The golden standard method of measuring arterial stiffness non-invasively is PW velocity (PWV) and augmentation index (AIx) by applanation tonometry of the arterial pressure PW [13]. AIx measures wave reflection and endothelial function. Applanation tonometry has been used for assessment of maternal vascular hemodynamics in pregnancy [5,14,15 16], where increased arterial stiffness and endothelial dysfunction are associated with increased risk of preeclampsia [17]. However, due to the complexity and unmanageability of methods for assessment of maternal central hemodynamics, brachial blood pressure (BP) monitoring is still the main way of evaluating cardiovascular status.

Digital PW analysis (DPA) by photoplethysmography (PPG) of the volume pulse wave is an operator independent, quick and easy method for assessment of arterial status. Changes of DPA parameters are associated with cardiovascular morbidity [18]. We have previously shown

Abbreviations: AI, aging index; APG, acceleration photoplethysmography; DPA, digital pulse wave analysis; PPG, photoplethysmography; PW, pulse wave

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good correlations between the tonometry variables PWV and AIx and DPA arterial stiffness parameters, as well as good repeatability between DPA measurements [19]. Studies on PPG in pregnancy are to this day scarce, however.

The aim of the study was to longitudinally investigate maternal arterial stiffness parameters assessed by digital photoplethysmographic PW analysis during normal pregnancy, and establish gestational age-adjusted reference values. Due to its operator simplicity, the DPA method is well suited for screening purposes, where such reference values could be used.

2. Methods

2.1. Study population

A total of 149 pregnant women were recruited at four different maternal health care service units in the vicinity of Malmö, Sweden. Inclusion criteria were pregnant women understanding Swedish, with no medical history of cardiovascular disease, ongoing medical treatment with vascular effect, multiple pregnancy, or kidney disease or diabetes at enrollment. Normotensive women with a history of hypertensive pregnancy, and women with medical treatment for asthma or thyroid disease, were accepted in the study. The study was approved by the Regional Research Ethics Committee in Lund (Dnr 2014/648) and all participants gave their oral and written informed consent.

2.2. Study protocol

Measurements were obtained longitudinally at 12–15, 20–24, 30, 37 and 41 gestational weeks during routine out-patient visits to the maternity clinics. Clinical data were registered upon the first visit. Gestational age (GA) was determined with first trimester or early second trimester ultrasound fetometry. Brachial BP was measured manually or with an automatic device. Mean arterial pressure (MAP) was calculated as diastolic BP + (systolic BP − diastolic BP)/3.

2.3. Arterial stiffness measurements

Arterial stiffness was measured by a Meridian DPA photoplethysmograph (Salcor AB, Uppsala, Sweden, www.meridian.co.kr), which provides 16 different indices for arterial stiffness. With a diode in a clip placed on the left index finger, light is emitted through the tissue and received by a photodiode at the opposite side and a PPG pulse curve is created with every pulse stroke by the difference in absorbed light relative to oxyhemoglobin content in the blood. With increased arterial stiffness, reflecting PWs from the peripheral vascular tree will return faster towards the heart and to a greater extent augment the forward-going PW and affect the contour of the composite PW. The crude PW contour is mathematically analyzed for assessment of arterial wall properties. An automatic mathematical remodeling of the crude PPG curve by second derivation, called “acceleration photoplethysmography” (APG), allows the pulse contour to be analyzed in further detail (Fig. 1). The APG consists of five distinct waves reflecting acceleration changes in the PPG curve, identified as *a*, *b*, *c*, *d*, and *e* waves and expressed as quotas of the *a*-wave, i.e. *b/a*, *c/a*, *d/a*, and *e/a*. The peak magnitude of quotas change by increased arterial wall stiffness correlated to aging [20]. Although a full comprehension of the APG is lacking, *b/a* has shown to be an indicator of left ventricular (LV) function and compliance in large arteries, and *d/a* of the magnitude of wave reflection from the periphery and effect of vasoactive drugs [20,21]. The APG aging index (AI) is calculated as (*b-c-d-e*)/*a* and is a composite global index representing ‘vascular age’. We chose the parameters AI, *b/a* and *d/a* for the study since they are correlated to arteriosclerosis, arterial disease and the Framingham risk score, and have been suggested as tools for evaluation of cardiovascular risk [20,22–24].

The DPA technique cannot separate structural (arterial wall remodeling) and physiological (vasoconstriction, volume expansion) alterations in compliance of arteries, and the term arterial stiffness is thus used independently of background in this paper.

Based on our previous findings on correlation to PWV and AIx measurements by applanation tonometry, and repeatability of the Meridian DPA variables [19], we chose to investigate DPA indices *b/a*, *d/a* and AI in the present study. These parameters are easily identified by APG and can be automatically calculated by any PPG apparatus equipped with APG. At each out-patient clinic visit two measurements à 70 s were performed after 10 min of rest in a supine position tilted slightly to the left, and the mean DPA value calculated. The women were instructed not to move or talk during measurements and asked to avoid large meals, caffeine and nicotine at least three hours before examination.

2.4. Statistical analyses

For analyses of associations between categorical and continuous variables, analysis of variance (ANOVA) or analysis of covariance (ANCOVA) were performed, as appropriate. For longitudinal comparisons, linear and polynominal mixed-effect models for repeated measurements were used up to the third degree to establish the simplest model with best fit. A two-tailed p value < 0.05 was regarded significant. Statistical analyses were performed using Gauss computer software (Gauss™, Aptech Systems, Inc., Maple Valley, WA, USA).

3. Results

Ten women were withdrawals (five due to development of hypertensive complications, one due to diagnosed IUGR, three due to multiple pregnancy, one due to technical problems and later miscarriage) and 139 women thus remained for statistical analyses. Three women stated they were smokers and five were former smokers, and one had a previous pregnancy complicated by hypertension. Three pregnancies were conceived by in vitro fertilization, five women miscarried, one had intrauterine fetal death at 28 weeks, and two pregnancies were terminated due to fetal malformations; one pregnancy was complicated by placental abruption and two by gestational diabetes.

Linear and quadratic mixed-effect models showed significant associations with GA for all DPA variables, with best fit for the quadratic models ($p < 0.001$, Fig. 2). Adjusting the DPA variables to a fixed HR of 82.72 bpm (mean value) did not significantly change the association with GA for any of the DPA variables. No significant differences in curve shapes depending on maternal age or parity were found in longitudinal measurements of any DPA variable ($p \geq 0.60$).

Since the majority of women had their first DPA monitoring at 14–16 weeks, and no major changes in mean value curve shapes were seen up to 24 gestational weeks for any of the DPA variables, we merged measurements performed at 14–24 weeks when calculating reference values. For women being monitored twice during this period, the mean values were calculated.

Table 1 shows normative data obtained at GA 14–24 weeks relative to maternal age and parity, and Table 2 shows the independent impact of maternal age and parity on DPA variables. When entering maternal age as a class variable (Table 2, ANOVA), *d/a* showed a small but significant reduction with age ($p = 0.01$, increased arterial stiffness) independent of parity, whereas AI and *b/a* did not change significantly with age. Independent of age, nulliparous women had significantly lower AI ($p = 0.006$, reduced stiffness) and *b/a* ($p = 0.016$, reduced stiffness) than parous women, but there was no significant difference in *d/a* relative to parity (Table 2, ANOVA).

When maternal age was entered as a continuous variable (Table 2, ANCOVA), five-year increments in maternal age resulted in significantly increasing AI ($p = 0.014$, increased stiffness) independent of parity, and the reduction in *d/a* was again statistically significant

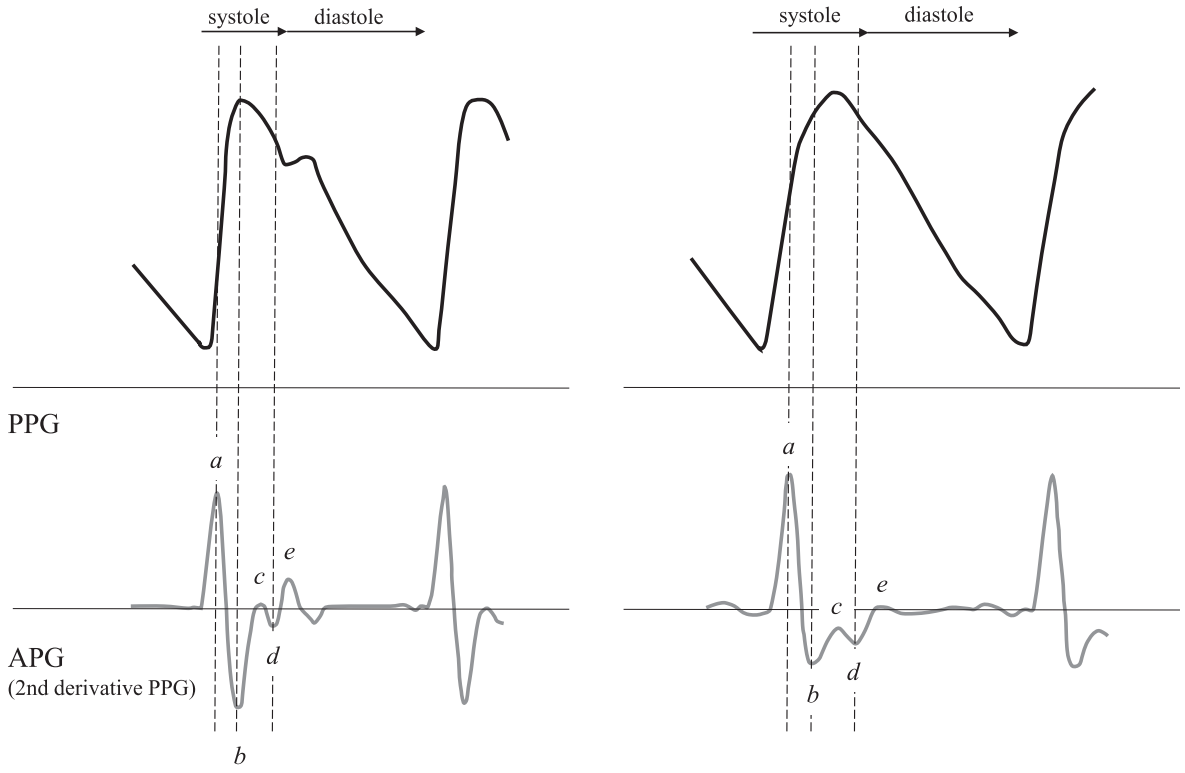

Fig. 1. Authentic digital photoplethysmografic volume pulse curve (PPG) (upper panel) and its corresponding second derivative acceleration photoplethysmogram (APG) (lower panel) from a 33 year old healthy woman (left) compared to equivalent registrations showing increased arterial stiffness from a 66 year old healthy man (right). The *b* wave corresponds to the first acceleration of blood flow into the aorta from the cardiac left ventricle in early systole, representing cardiac ejection power and/or aortal compliance. The *d* wave corresponds to the intensity of the reflected wave from the periphery in late systole, indicative of afterload dependent on peripheral vascular resistance.

($p = 0.001$, increased stiffness). The differences in AI ($p = 0.007$) and b/a ($p = 0.026$) in nulliparous vs. parous women were also significant.

4. Discussion

This study showed significant changes in arterial wall stiffness with progression of pregnancy, indicating an increased compliance in central and peripheral arteries from the first trimester, reaching its maximum

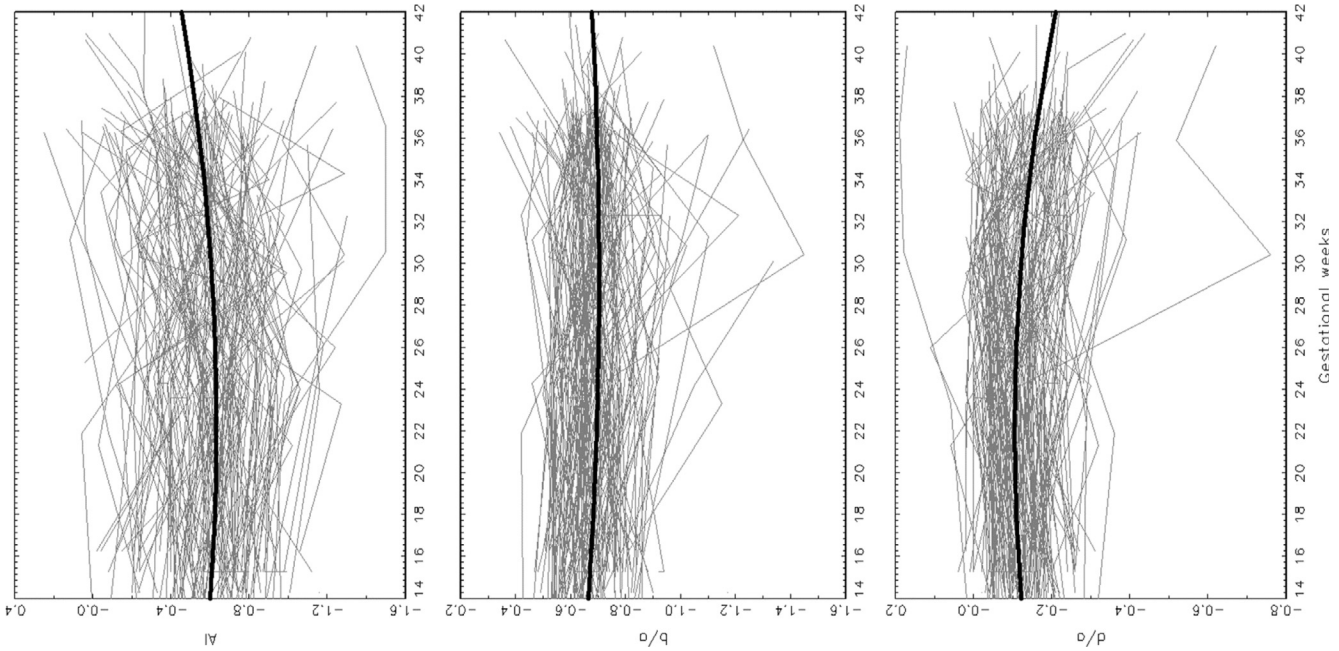

Fig. 2. Associations between maternal aging index (AI), b/a and d/a, and gestational age in 139 uncomplicated pregnancies. The associations were significant ($p < 0.001$) when calculated with quadratic mixed-effects models.

Table 1
Distributions of aging index (AI), *b/a*, *d/a*, and mean arterial blood pressure among 139 women monitored between gestational weeks 14 and 24 (mean 17.5 weeks, median 15 weeks, inter quartile range 14–23.5).

			Percentiles						Mean	(95%CI)
	n	2.5	5	25	50	75	95	97.5		
AI										
Total	139	−1.16	−1.06	−0.77	−0.62	−0.45	−0.14	−0.04	−0.62	(−0.66, −0.57)
Maternal age (years)										
< 25	13			−0.92	−0.66	−0.57			−0.72	(−0.84, −0.60)
25–29	40			−0.80	−0.72	−0.56			−0.67	(−0.75, −0.60)
30–34	50			−0.78	−0.60	−0.42			−0.61	(−0.69, −0.52)
35–39	32			−0.64	−0.54	−0.40			−0.54	(−0.64, −0.44)
40+	4			−0.81	−0.36	−0.28			−0.43	(−0.79, −0.08)
Parity										
Nulliparae	51	−1.15	−1.08	−0.86	−0.72	−0.57	−0.31	−0.27	−0.71	(−0.77, −0.65)
Multiparae	82	−1.23	−1.04	−0.73	−0.59	−0.40	−0.05	0.03	−0.55	(−0.61, −0.50)
b/a										
Total	139	−0.93		−0.76	−0.66	−0.59		−0.48	−0.68	(−0.70, −0.66)
Maternal age (years)										
< 25	13			−0.77	−0.71	−0.58			−0.70	(−0.77, −0.63)
25–29	40			−0.78	−0.70	−0.60			−0.70	(−0.73, −0.66)
30–34	50			−0.76	−0.64	−0.56			−0.67	(−0.71, −0.63)
35–39	32			−0.74	−0.66	−0.56			−0.67	(−0.72, −0.62)
40+	4			−0.72	−0.56	−0.52			−0.60	(−0.79, −0.42)
Parity										
Nulliparae	51	−0.91	−0.90	−0.80	−0.72	−0.56	−0.54	−0.52	−0.72	(−0.75, −0.68)
Multiparae	82	−1.13	−0.86	−0.73	−0.64	−0.56	−0.52	−0.44	−0.65	(−0.68, −0.63)
d/a										
Total	139	−0.29	−0.26	−0.16	−0.11	−0.06	0.02	0.04	−0.11	(−0.13, −0.10)
Maternal age (years)										
< 25	13			−0.10	−0.08	−0.06			−0.07	(−0.11, −0.02)
25–29	40			−0.12	−0.09	−0.05			−0.10	(−0.12, −0.08)
30–34	50			−0.16	−0.11	−0.06			−0.11	(−0.13, −0.09)
35–39	32			−0.20	−0.15	−0.08			−0.15	(−0.18, −0.12)
40+	4			−0.26	−0.14	−0.11			−0.19	(−0.32, −0.05)
Parity										
Nulliparae	51	−0.22	−0.21	−0.13	−0.10	−0.06	0.04	0.06	−0.10	(−0.12, −0.08)
Multiparae	82	−0.32	−0.29	−0.18	−0.11	−0.07	0.04	0.00	−0.13	(−0.15, −0.11)
Mean arterial pressure (mmHg)										
Total	133	70.0	71.4	76.7	82.0	86.7	95.0	97.2	82.3	(81.1–83.6)
Maternal age (years)										
< 25	13			72.5	75.0	82.5			78.4	(73.5, 83.3)
25–29	38			76.7	83.3	86.7			82.3	(80.2, 84.5)
30–34	48			77.1	83.3	90.0			82.9	(80.9, 84.9)
35–39	30			76.7	82.0	85.7			82.2	(79.1, 85.3)
40+	4			83.3	91.7	94.2			88.8	(77.8, 99.7)
Parity										
Nulliparae	49	66.5	70.8	76.7	83.3	87.0	95.0	98.8	82.5	(80.3, 84.6)
Multiparae	79	70.0	70.7	76.7	81.3	86.7	95.0	97.3	82.2	(80.6, 83.9)

CI, confidence interval. Digital pulse wave analysis values are indices without quantitative measures.

Table 2
The impact of maternal age and parity on values of aging index (AI), *b/a*, and *d/a*, respectively, at measurements in gestational weeks 14 to 24 (n = 139).

Results from ANOVA	AI			*b/a*			*d/a*		
	Contrast	95%CI	*p*	Contrast	95%CI	*p*	Contrast	95%CI	*p*
Maternal age (years)									
< 25	0	Reference	0.127	0	Reference	0.670		Reference	0.01
25–29	0.03	−0.12, 0.18		0.00	−0.08, 0.08		−0.03	−0.08, 0.02	
30–34	0.08	−0.08, 0.24		0.02	−0.06, 0.10		−0.04	−0.09, 0.01	
35–39	0.14	−0.03, 0.32		0.02	−0.07, 0.11		−0.08	−0.13, −0.02	
40+	0.28	−0.01, 0.56		0.10	−0.05, 0.24		−0.12	−0.20, −0.03	
Parity									
Multiparae	0	Reference	0.006	0	Reference	0.016	0	Reference	0.222
Nulliparae	−0.13	−0.22, −0.04		−0.06	−0.10, −0.01		0.02	−0.01, 0.05	
Results from ANCOVA	Beta	95%CI	*p*	Beta	95%CI	*p*	Beta	95%CI	*p*
Increase per five year maternal age increment	0.06	0.01, 0.11	0.014	0.02	−0.01, 0.04	0.136	−0.03	−0.04, −0.01	0.001
Nulliparae vs. multiparae	−0.12	−0.22, −0.04	0.007	−0.05	−0.10, −0.01	0.026	0.02	−0.01, 0.04	0.284

ANOVA, analysis of variance (maternal age entered as class variable); ANCOVA, analysis of covariance (maternal age entered as continuous variable).

in the late second trimester, and thereafter decreasing towards term. The DPA variables were independently related to both maternal age and parity, but differences in age and parity did not alter the variations with gestational age. Although the slopes of the DPA variable curves changed significantly over time, the changes were small relative to the overall variations in DPA values. Therefore, we suggest that DPA reference values for normal second and third trimester pregnancy can be used independent of GA. There were minimal changes in DPA mean values up to about 24 weeks and we therefore restricted the calculation of reference values to 14–24 gestational weeks. The alternative to calculate DPA values averaged over full gestation would have reduced precision in the first period, which is the relevant period for potential screening with DPA for preeclampsia and IUGR.

Although the DPA variable changes over gestation were small, they were in congruence with previously reported TVR changes in pregnancy [25]. TVR, which is the quota of MAP and CO, reflects vascular tone of resistance vessels and blood viscosity. TVR and arterial compliance are closely related, where TVR is the steady component and arterial compliance the pulsatile component of cardiac afterload. In normal pregnancy, TVR is decreased and arterial compliance increased, why CO can be increased without major changes in MAP [2]. This crucial hemodynamic adaption appears confirmed by the photoplethysmographic DPA method used in our study.

The longitudinal DPA variable changes were as well in congruence with the gestational pattern of pressure PW-derived AIx measurements obtained in cross-sectional [26,27] and longitudinal [5,15,16] tonometry studies in normal pregnancy, and with arterial stiffness indices obtained by volume PW-derived PPG [28,29].

The APG variable b/a reflects the acceleration phase of blood ejected from the left cardiac ventricle (LV) into the aorta and is thus an indicator of LV function and aortic compliance. b/a changed from early pregnancy towards an increased central artery compliance, alternatively increased LV ejection power. It is not possible with the DPA technique to determine if the b/a change attributes to cardiac or central arterial alterations, or both. Studies of the maternal heart in normal pregnancy show remodeling with increased cardiac dimensions and LV mass, but findings concerning systolic function are not unanimous [2].

Parity and pregnancy intervals have been reported to influence cardiovascular response to pregnancy. The aorta is larger and more compliant in parous than in nulliparous women [30], and parous women show significantly higher CO and lower TVR and MAP [31,32]. These changes may be attributed to vascular imprinting by the first pregnancy [32]. However, by AI and b/a measurements we found that parous women, independent of age, had increased arterial stiffness, or possibly reduced LV performance, compared to nulliparous women. d/a indicated however no difference in peripheral artery stiffness or afterload. The results then seem opposed to previous research, though those studies were performed with other modalities; we found in the literature no previous studies with PW analysis that could enlighten us. If and how parity impacts arterial elasticity is an interesting issue to be elucidated in future studies.

We have previously shown significant but weak correlations between DPA indices and HR [19], and the HR increases during pregnancy [2]. However, adjusting the reference values for HR did not change the DPA associations to GA in this study and is then not indicated.

A strength of the study is the relatively large study group compared to other longitudinal studies with PW analysis in pregnancy. Our study sample size thus fulfilled the requirement for determination of reference values recommended by the International Federation of Clinical Chemistry [33]. Since the greatest change in maternal arterial compliance occurs in the first trimester [4], it would have been desirable to obtain DPA reference values also in early pregnancy, but that was not possible because within the regular maternal health care program women are booked in the late first or early second trimester of pregnancy. In a recent study on women with in vitro fertilization, we found no significant changes of DPA variables in gestational week seven compared to pre-conceptional values [34].

In summary, the study showed that arterial stiffness in large and small arteries significantly changed with gestational age in uncomplicated pregnancy. However, the changes were minor in comparison with individual variations, why we suggest that gestational week must not be considered in future studies in the second and third trimesters of pregnancy using DPA for vascular assessment. We provide reference values of the APG indices AI, b/a and d/a obtained longitudinally in normal pregnancy by a quick and operator-independent PW analysis method, well aimed for screening purposes. There is growing evidence that normal hemodynamic adaption to pregnancy, and even the cardiovascular status before pregnancy, play a crucial role for normal pregnancy development. Pregnancy complications such as preeclampsia and IUGR seem associated with maternal cardiovascular structural and functional abnormalities [6,35], and gestational hypertension, early- and late-onset preeclampsia and IUGR, are characterized by different hemodynamic profiles [36–39]. This has awoken the interest in maternal hemodynamic evaluation for prediction of pregnancy complications, and several studies have reported promising results [8,40–43]. Whether DPA could be a tool for evaluation of pathological hemodynamic processes in pregnancy remains to be investigated.

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Conflict of interest

The authors state no conflict of interest.

Contributions

All authors have substantially contributed to the paper. Planning and conducting the study: EvW, PO. Analyzing and interpreting data, writing the manuscript: EvW, KK, PO. The study was supported by grants from Region Skåne and the Medical Faculty (ALF), Lund University, Sweden.

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