Check for updates

Ultrasound Obstet Gynecol 2021; **58**: 285–292
Published online in Wiley Online Library (wileyonlinelibrary.com). **DOI:** 10.1002/uog.23614

Effect of maternal age on cardiac adaptation in pregnancy

H. Z. LING, P. GARCIA JARA, K. H. NICOLAIDES and N. A. KAMETAS

Fetal Medicine Research Institute, King's College Hospital, London, UK

KEYWORDS: adaptation; bioreactance; cardiac output; hemodynamics; maternal age; peripheral vascular resistance

CONTRIBUTION

What are the novel findings of this work?
With increasing maternal age, there is a decrease in cardiac output and an increase in peripheral vascular resistance throughout pregnancy. The higher cardiac output in younger women was achieved through an increase in heart rate and not stroke volume. Despite better cardiac adaptation, younger women had the highest prevalence of a small-for-gestational-age neonate among all age groups.

What are the clinical implications of this work?
Age-specific differences in maternal hemodynamic adaptation alone do not explain the higher prevalence of a small-for-gestational-age neonate in the youngest age group.

ABSTRACT

Objective *To compare longitudinal maternal hemodynamic changes throughout gestation between different age groups.*

Methods *This was a prospective longitudinal study assessing maternal hemodynamics using a bioreactance technique at 11 + 0 to 13 + 6, 19 + 0 to 24 + 0, 30 + 0 to 34 + 0 and 35 + 0 to 37 + 0 weeks' gestation. Women were divided into four groups according to maternal age at the first visit at 11 + 0 to 13 + 6 weeks: Group 1, < 25.0 years; Group 2, 25.0–30.0 years; Group 3, 30.1–34.9 years; and Group 4, ≥ 35.0 years. A multilevel linear mixed-effects model was performed to compare the repeat measurements of hemodynamic variables, correcting for demographics, medical and obstetric history, pregnancy complications, maternal age and gestational-age window.*

Results *The study population included 254 women in Group 1, 442 in Group 2, 618 in Group 3 and 475 in Group 4. Younger women (Group 1) had the highest cardiac output (CO) and lowest peripheral vascular resistance (PVR), and older women (Group 4) had the lowest CO and highest PVR throughout pregnancy. The higher CO seen in younger women was achieved through an increase in heart rate alone and not with a concomitant rise in stroke volume. Although the youngest age group demonstrated an apparently more favorable hemodynamic profile, it had the highest incidence of a small-for-gestational-age neonate. There was no significant difference between the groups in the incidence of pre-eclampsia.*

Conclusion *Age-specific differences in maternal hemodynamic adaptation do not explain the differences in the incidence of a small-for-gestational-age neonate between age groups.* © *2021 International Society of Ultrasound in Obstetrics and Gynecology.*

INTRODUCTION

A rising trend in delayed childbearing has become increasingly common, driven by changes in socioeconomic demographics, improved education and career opportunities and advancement in assisted reproductive techniques[1,2]. Previous studies examining the association between maternal age and adverse pregnancy outcome have reported contradictory findings. Both extremes of the reproductive age are considered at increased risk for adverse outcome[3]. Teenage mothers have a higher risk of preterm delivery, birth of a small-for-gestational-age (SGA) neonate, low Apgar score and postnatal mortality[4]. It is uncertain whether this association is due to biological immaturity, socioeconomic disadvantages or behavioral factors[5,6]. On the other hand, most studies reported an association between advanced maternal age and preterm delivery, birth of a SGA neonate and perinatal death[7–11].

A pathological hemodynamic profile, such as low cardiac output (CO) and high peripheral vascular resistance (PVR), has been shown to be associated with pregnancy-related complications, such as pre-eclampsia (PE) and birth of a SGA neonate[12–16]. However, it is

Correspondence to: Dr N. A. Kametas, Fetal Medicine Research Institute, King's College Hospital, 16–20 Windsor Walk, Denmark Hill, London SE5 8BB, UK (e-mail: nick.kametas@kcl.ac.uk)

Accepted: 8 February 2021

© 2021 International Society of Ultrasound in Obstetrics and Gynecology.

unclear to what extent maternal age affects cardiovascular response to pregnancy. Age-associated cardiovascular changes include a complex interaction between the preload, the heart as a pump and the afterload imposed on the heart by the arterial system[17]. The biological effects of aging include a reduction in vascular compliance, impaired endothelial-dependent vasodilatation and hypertension[18,19]. Furthermore, cardiac aging is associated with myocyte loss and mild hypertrophy with reduced sensitivity to sympathetic stimuli, resulting in reduced pumping ability[20]. In pregnancy, some studies suggested a possible correlation between maternal age and an increase in mean uterine artery pulsatility index[21], arterial stiffness, systemic vascular resistance[22] and diastolic blood pressure[23]. Although these studies are suggestive of cardiac and vascular dysfunction in women of advanced age, there remain limited data regarding the impact of maternal age on longitudinal maternal hemodynamics and the mechanism of cardiac maladaptation.

The objective of this study was to compare longitudinal maternal hemodynamic changes throughout gestation between different age groups.

METHODS

Study population

Between November 2015 and May 2016, all women with singleton pregnancy who attended routine pregnancy care at 11 + 0 to 13 + 6 weeks' gestation in six maternity hospitals were invited to participate in this study. Longitudinal maternal hemodynamic and fetal assessments were performed at four visits at 11 + 0 to 13 + 6, 19 + 0 to 24 + 0, 30 + 0 to 34 + 0 and 35 + 0 to 37 + 0 weeks' gestation. Gestational age was confirmed by measurement of fetal crown–rump length[24]. Pregnancies with a fetal anomaly, those that resulted in miscarriage or termination, those that had poor signals and those with missing pregnancy outcome were excluded. During each of the visits, we enquired about the development of any pregnancy complications, measured maternal weight and blood pressure and assessed cardiovascular function non-invasively. The study was approved by the NHS Research Ethics Committee (REC reference: 13/LO/1479).

Maternal factors and pregnancy outcome

Maternal factors recorded included age, height, weight, body surface area, racial origin (white, black, South Asian, East Asian or mixed), method of conception (natural or use of assisted reproductive technologies), cigarette smoking, medical history (chronic hypertension, diabetes mellitus or asthma) and parity (nulliparous or parous with or without previous PE or SGA). Pregnancy outcomes included PE, gestational age at delivery and birth weight.

Maternal cardiac function was assessed using a non-invasive bioreactance method (NICOM, Cheetah Medical Ltd, Maidenhead, Berkshire, UK). We have validated previously the NICOM monitor for use in pregnancy by comparing it against echocardiography across the three trimesters[25]. The bioreactance technology utilizes simultaneous relative phase shifts to calculate stroke volume (SV) when an alternating electrical current traverses the thoracic cavity. We applied the four electrodes across the woman's back after 15 min of rest, and cardiac variables (CO, SV, heart rate (HR), PVR and mean arterial pressure (MAP)) were recorded with the woman in a sitting position over a 10-min period at 30-s intervals (20 cycles). Analysis of hemodynamic variables included the averages of the measurements from the final 10 cycles.

Definitions

We classified the study population into four groups based on maternal age at booking: Group 1, < 25.0 years; Group 2, 25.0–30.0 years; Group 3, 30.1–34.9 years; and Group 4, ≥ 35.0 years. Birth-weight percentile for gestational age was derived from the Fetal Medicine Foundation reference range[26]. The definitions of PE and gestational hypertension (GH) were those of the International Society for the Study of Hypertension in Pregnancy[27].

Statistical analysis

We examined the longitudinal changes of maternal cardiovascular variables stratified according to maternal age at booking, as described above. Maternal demographic and pregnancy outcome characteristics were compared between the four groups. For continuous data, the Kruskal–Wallis or one-way ANOVA test was used for non-normally and normally distributed data, respectively. For the comparison of categorical data, the chi-square test was used. The Kolmogorov–Smirnov test was used to assess the normality of the distribution of numerical data. Data are presented as median (interquartile range) or mean ± SD for non-normally and normally distributed continuous variables, respectively, and as *n* (%) for categorical variables. The distributions of maternal weight, CO, SV, MAP and PVR were made Gaussian after $\log_{10}$ transformation.

For the maternal hemodynamic variables, we performed a multilevel linear mixed-effects model for repeated-measures analyses, as these models are more robust when dealing with missing values in longitudinal studies, compared to traditional repeated-measures ANOVA. We controlled for $\log_{10}$ maternal weight at booking, height, racial origin, smoking, asthma, previous PE or SGA, parity, maternal medical conditions (chronic hypertension and diabetes), pregnancy-related complications, such as PE, GH and gestational diabetes, method of conception (natural or by assisted reproductive techniques), maternal age group, gestational-age window (i.e. the four visits) and the interaction between maternal age group and gestational age at assessment. The likelihood ratio test was used to define the best multilevel model comparing the base model to either the random

© 2021 International Society of Ultrasound in Obstetrics and Gynecology.

14690705, 2021, 2, Downloaded from https://obgyn.onlinelibrary.wiley.com/doi/10.1002/uog.23614 by <Shibboleth>-member@kcl.ac.uk, Wiley Online Library on [31/10/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

intercept or random intercept and slope. The estimated marginal means of each hemodynamic variable for each maternal age group and gestational age combination are presented.

The software program IBM SPSS Statistics 26 for Windows (IBM Corp., Armonk, NY, USA) was used for statistical analyses.

RESULTS

A total of 1918 women (99% of those approached) agreed to participate in the study. After the first visit, 13 pregnancies were diagnosed with a fetal anomaly, and 16 resulted in subsequent miscarriage or termination due to fetal abnormality. After further excluding women with poor signals or missing pregnancy outcome and those who withdrew their consent to participate in the study, a total of 1789 women were followed up at the four visits (Figure 1). From the total cohort, 100%, 88%, 87% and 86% of women attended Visits 1–4, respectively. The four groups included 254 women in Group 1, 442 in Group 2, 618 in Group 3 and 475 in Group 4.

Maternal demographics and pregnancy outcome

The maternal demographic characteristics and pregnancy outcome for the four maternal-age groups are presented in Table 1. Compared with Group 1, women in Groups 2–4 were taller and less likely to be smokers or nulliparous, whilst women in Groups 3 and 4 were at least twice as likely to have conceived by assisted reproductive techniques. Women in Group 4 were four times more likely to have chronic hypertension or pre-existing diabetes than those in Group 2, whilst women in Group 1 were five times and twice as likely to have asthma compared to Groups 2 and 3, respectively. There was no significant difference in maternal weight at booking or racial origin amongst the four groups. Birth-weight percentile in Groups 3 and 4 was significantly higher than

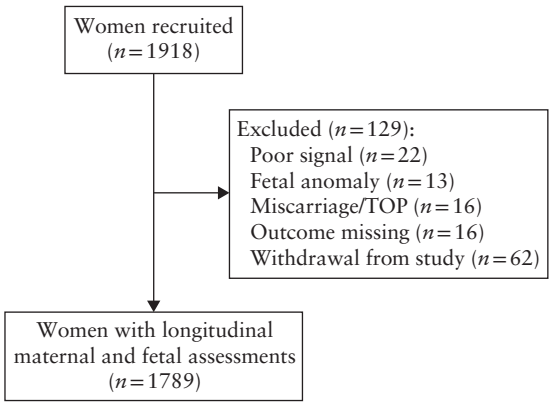

Figure 1 Flowchart of study recruitment. TOP, termination of pregnancy.

Table 1 Demographic characteristics and pregnancy outcomes of the study population of 1789 pregnancies, according to maternal age

Variable	*Group 1* (*< 25.0 years*) (n = *254*)	*Group 2* (*25.0–30.0 years*) (n = *442*)	*Group 3* (*30.1–34.9 years*) (n = *618*)	*Group 4* (*≥ 35.0 years*) (n = *475*)	P
Age (years)	22.8 (20.9–24.1)	27.7 (26.5–28.9)***	32.4 (31.3–33.7)***†††‡‡‡	37.0 (35.0–38.6)***†††	< 0.0001
Height (cm)	163 ± 6.3	165 ± 6.6*	165 ± 6.6***	165 ± 6.7*	< 0.0001
Weight (kg)	67.6 (57.0–82.9)	69.0 (60.2–81.4)	67.0 (60.4–79.0)	68.4 (61.0–78.6)	0.293
Body mass index (kg/m^2)	26.8 ± 6.5	26.6 ± 5.7	25.7 ± 4.9*†	26.5 ± 5.3	0.011
Body surface area (m^2)	1.7 (1.6–1.9)	1.8 (1.6–1.9)	1.7 (1.6–1.9)	1.8 (1.7–1.9)	0.168
Smoker	34 (13.4)	35 (7.9)*	20 (3.2)***††	7 (1.5)***†††	< 0.0001
Racial origin					0.419
White	187 (73.6)	329 (74.4)	459 (74.3)	347 (73.1)	
Black	36 (14.2)	73 (16.5)	92 (14.9)	76 (16.0)	
South Asian	15 (5.9)	19 (4.3)	39 (6.3)	25 (5.3)	
East Asian	3 (1.2)	9 (2.0)	12 (1.9)	16 (3.4)	
Mixed	13 (5.1)	12 (2.7)	16 (2.6)	11 (2.3)	
Nulliparous	181 (71.3)	235 (53.2)***	317 (51.3)***‡‡	200 (42.1)***††	< 0.0001
Parous					< 0.0001
Previous PE or SGA	16 (6.3)	33 (7.5)	32 (5.2)	37 (7.8)	
No previous PE or SGA	57 (22.4)	174 (39.4)	269 (43.5)	238 (50.1)	
Conception by ART	0 (0)	2 (0.5)	14 (2.3)*†‡‡	27 (5.7)***†††	< 0.0001
Chronic hypertension	5 (2.0)	4 (0.9)	8 (1.3)‡‡	20 (4.2)††	0.001
Pre-existing diabetes	0 (0)	2 (0.5)	3 (0.5)‡	9 (1.9)*†	0.012
Asthma	12 (4.7)	4 (0.9)**	12 (1.9)*	11 (2.3)	0.010
Gestational age at birth (weeks)	39.6 (38.7–40.6)	39.9 (38.9–40.7)	40.0 (39.0–41.0)*‡‡	39.7 (38.9–40.6)	0.003
PE	7 (2.8)	14 (3.2)	18 (2.9)	14 (2.9)	0.991
Birth-weight percentile	38.6 (13.8–68.4)	43.1 (18.6–74.0)	49.5 (23.3–72.8)**	49.8 (22.6–76.1)**	0.011
Birth weight < 10th percentile	52 (20.5)	68 (15.4)	70 (11.3)***	71 (14.9)	0.006
Birth weight > 90th percentile	16 (6.3)	41 (9.3)	61 (9.9)	46 (9.7)	0.386

Data are given as median (interquartile range), mean ± SD or *n* (%). Compared to Group 1: *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$. Compared to Group 2: †$P < 0.05$; ††$P < 0.01$; †††$P < 0.0001$. Compared to Group 4: ‡$P < 0.05$; ‡‡$P < 0.01$; ‡‡‡$P < 0.0001$. ART, assisted reproductive technique; PE, pre-eclampsia; SGA, small-for-gestational age.

© 2021 International Society of Ultrasound in Obstetrics and Gynecology.

14690705, 2021, 2, Downloaded from https://obgyn.onlinelibrary.wiley.com/doi/10.1002/uog.23614 by <Shibboleth>-member@kcl.ac.uk, Wiley Online Library on [31/10/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Table 2 Fixed and random effects of multilevel linear mixed-effects models for maternal log_{10} cardiac output, log_{10} peripheral vascular resistance (PVR), heart rate, log_{10} stroke volume and log_{10} mean arterial pressure (MAP)

	Log_{10} cardiac output		*Log_{10}PVR*		*Heart rate*		*Log_{10} stroke volume*		*Log_{10}MAP*	
Parameter	*Estimate ± SE*	P	*Estimate ± SE*	P	*Estimate ± SE*	P	*Estimate ± SE*	P	*Estimate ± SE*	P
Fixed part										
Intercept	−0.056 ± 0.050	0.263	3.652 ± 0.050	< 0.0001	98.419 ± 5.714	< 0.0001	0.942 ± 0.057	< 0.0001	1.669 ± 0.021	< 0.0001
Height (in cm)	0.003 ± 0.000	< 0.0001	−0.003 ± 0.000	< 0.0001	−0.211 ± 0.032	< 0.0001	0.004 ± 0.001	< 0.0001	−0.000 ± 0.000	0.021
Log_{10} weight (in kg)	0.151 ± 0.021	< 0.0001	—	NS	13.149 ± 2.339	< 0.0001	0.093 ± 0.025	< 0.0001	0.174 ± 0.009	< 0.0001
Smoker (ref, non-smoker)	—	NS	—	NS	—	NS	—	NS	−0.011 ± 0.003	< 0.0001
Race (ref, white)										
Black	−0.010 ± 0.004	0.024	0.011 ± 0.005	0.030	2.314 ± 0.549	< 0.0001	−0.024 ± 0.005	< 0.0001	—	NS
South Asian	−0.029 ± 0.007	< 0.0001	0.025 ± 0.008	0.005	1.744 ± 0.886	0.049	−0.038 ± 0.008	< 0.0001	—	NS
East Asian	−0.043 ± 0.011	< 0.0001	0.037 ± 0.013	0.005	0.727 ± 1.325	0.583	−0.049 ± 0.012	< 0.0001	—	NS
Mixed	−0.012 ± 0.010	0.228	0.002 ± 0.011	0.808	−0.902 ± 1.157	0.436	−0.007 ± 0.011	0.522	—	NS
Parity (ref, nulliparous)										
Parous, previous PE or SGA	0.015 ± 0.006	0.027	−0.011 ± 0.007	0.150	1.448 ± 0.800	0.071	—	NS	0.002 ± 0.003	0.455
Parous, no previous PE or SGA	0.013 ± 0.003	< 0.0001	−0.024 ± 0.004	< 0.0001	1.315 ± 0.410	0.001	—	NS	−0.008 ± 0.001	< 0.0001
MA group (ref, Group 4 (≥ 35.0 years))										
Group 1 (< 25.0 years)	0.036 ± 0.005	< 0.0001	−0.044 ± 0.006	< 0.0001	6.141 ± 0.644	< 0.0001	—	NS	—	NS
Group 2 (25.0–30.0 years)	0.024 ± 0.004	< 0.0001	−0.028 ± 0.005	< 0.0001	2.734 ± 0.542	< 0.0001	—	NS	—	NS
Group 3 (30.1–34.9 years)	0.008 ± 0.004	0.047	−0.010 ± 0.005	0.044	1.425 ± 0.502	0.005	—	NS	—	NS
Hypertensive disorder (ref, none)										
Pre-eclampsia	−0.014 ± 0.009	0.141	—	NS	—	NS	—	NS	—	NS
Gestational hypertension	−0.027 ± 0.009	0.003	—	NS	—	NS	—	NS	—	NS
Chronic hypertension	−0.018 ± 0.013	0.158	—	NS	—	NS	—	NS	—	NS
Conception by ART	—	NS	—	NS	—	NS	—	NS	—	NS
Pre-existing diabetes	—	NS	—	NS	—	NS	—	NS	—	NS
Gestational diabetes	—	NS	—	NS	—	NS	—	NS	—	NS
Asthma	—	NS	—	NS	—	NS	—	NS	—	NS
GA window	—	< 0.0001	—	< 0.0001	—	< 0.0001	—	< 0.0001	—	< 0.0001
Interaction (MA and GA)	—	NS	—	NS	—	NS	—	NS	—	NS
Random part										
Within subject (residual)	0.008 ± 0.002	< 0.0001	0.009 ± 0.002	< 0.0001	43.356 ± 0.894	< 0.0001	0.009 ± 0.002	< 0.0001	0.008 ± < 0.0001	< 0.0001
Between subject	0.003 ± 0.002	< 0.0001	0.004 ± 0.002	< 0.0001	53.100 ± 2.232	< 0.0001	0.003 ± 0.002	< 0.0001	0.008 ± < 0.0001	< 0.0001

ART, assisted reproductive techniques; GA, gestational age; MA, maternal age; NS, not significant; PE, pre-eclampsia; ref, reference; SE, standard error; SGA, small-for-gestational age.

© 2021 International Society of Ultrasound in Obstetrics and Gynecology.

14690705, 2021, 2, Downloaded from https://obgyn.onlinelibrary.wiley.com/doi/10.1002/uog.23614 by <Shibboleth>-member@kcl.ac.uk, Wiley Online Library on [31/10/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

that in Group 1. The highest incidence of a SGA neonate was in Group 1. There was no significant difference between the groups in the incidence of PE.

Multilevel linear mixed-effects models

The fixed effects of the best multilevel models for log_{10}CO, log_{10}PVR, HR, log_{10}SV and log_{10}MAP are shown in Table 2, and the estimated marginal means are shown in Table 3 and Figure 2. For log_{10}CO, HR and log_{10}PVR, a random-intercept model provided a significantly better fit to the data than did the base model or a random intercept–random slope model based on the likelihood radio test. There was no difference between the groups in log_{10}SV or log_{10}MAP. Compared to an empty model containing only random effects, the full model including the fixed and random effects led to a reduction in residual variance by 4.3%, 4.7%, 1.2%, 5.8% and 27.7%

Table 3 Estimated marginal means of antilog values for maternal cardiac parameters from multilevel linear mixed-effects models in the study population at four visits throughout gestation, according to maternal age

Parameter	*Group 1 (< 25.0 years)*	*Group 2 (25.0–30.0 years)*	*Group 3 (30.1–34.9 years)*	*Group 4 (≥ 35.0 years)*
Cardiac output (L/min) at:				
11–14 weeks	5.56 (5.38–5.75)	5.42 (5.25–5.58)*	5.22 (5.08–5.38)***†‡‡	5.12 (4.97–5.27)***†††
19–24 weeks	5.93 (5.74–6.14)	5.77 (5.59–5.94)*	5.57 (5.41–5.73)***†‡‡	5.45 (5.29–5.62)***†††
30–34 weeks	6.08 (5.87–6.29)	5.91 (5.72–6.09)*	5.71 (5.55–5.87)***†‡‡	5.59 (5.43–5.76)***†††
35–37 weeks	5.89 (5.69–6.09)	5.73 (5.55–5.92)*	5.53 (5.37–5.70)***†‡‡	5.42 (5.26–5.58)***†††
PVR (dynes × s/cm^{-5}) at:				
11–14 weeks	1233.11 (1193.99–1270.57)	1279.38 (1244.52–1315.23)*	1333.52 (1300.17–1367.73)***††‡‡	1364.58 (1330.45–1402.81)***†††
19–24 weeks	1124.61 (1091.44–1161.45)	1169.50 (1137.63–1199.50)*	1218.99 (1188.50–1250.26)***††‡‡	1247.38 (1216.19–1282.33)***†††
30–34 weeks	1091.44 (1059.25–1127.19)	1135.01 (1104.08–1164.13)*	1183.04 (1153.45–1213.39)***††‡‡	1210.59 (1180.32–1255.51)***†††
35–37 weeks	1148.15 (1114.29–1185.77)	1193.98 (1161.45–1227.44)*	1244.52 (1213.39–1276.44)***††‡‡	1273.50 (1241.65–1309.18)***†††
Heart rate (bpm) at:				
11–14 weeks	88.6 (87.3–89.9)	85.2 (84.1–86.3)***	83.9 (82.8–84.9)***†‡‡	82.5 (81.4–83.6)***†††
19–24 weeks	91.7 (90.4–93.1)	88.4 (87.2–89.5)***	87.1 (85.9–88.1)***†‡‡	85.6 (84.5–86.7)***†††
30–34 weeks	96.3 (94.9–97.6)	92.8 (91.7–94.0)***	91.6 (90.5–92.6)***†‡‡	90.1 (89.0–91.2)***†††
35–37 weeks	96.1 (94.8–97.5)	92.7 (91.6–93.9)***	91.4 (90.4–92.5)***†‡‡	90.0 (88.9–91.1)***†††

Values in parentheses are 95% CI. Compared to Group 1: *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$. Compared to Group 2: †$P < 0.05$; ††$P < 0.01$; †††$P < 0.0001$. Compared to Group 4: ‡$P < 0.05$; ‡‡$P < 0.01$; ‡‡‡$P < 0.0001$. PVR, peripheral vascular resistance.

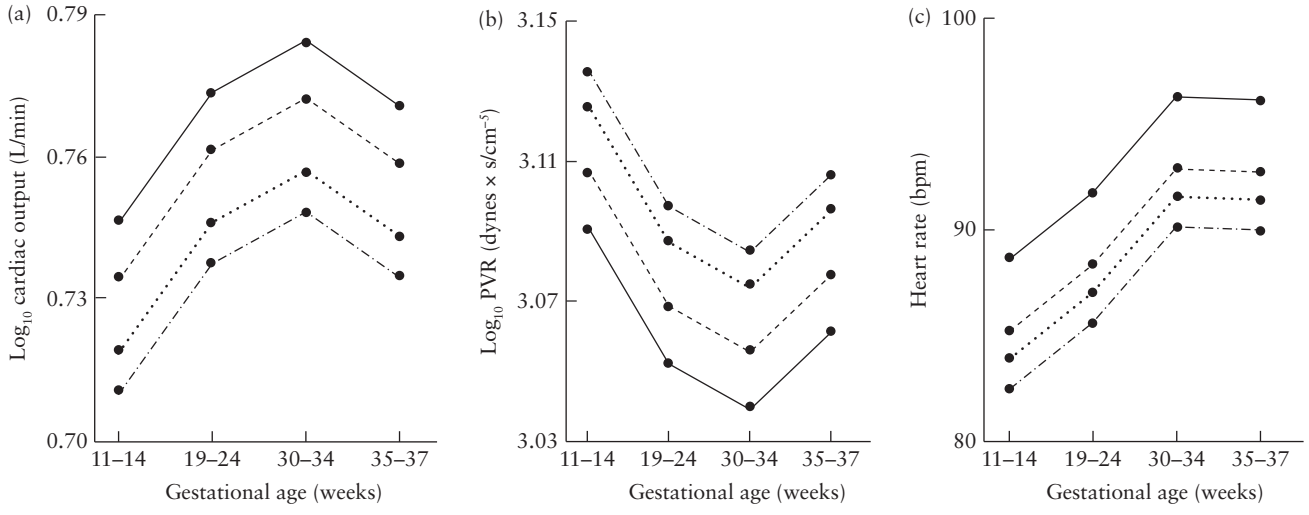

Figure 2 Linear mixed-effects model with estimated marginal means for maternal log_{10} cardiac output (a), log_{10} peripheral vascular resistance (PVR) (b) and heart rate (c), after controlling for demographic characteristics, at four visits throughout gestation, according to maternal age: Group 1, < 25.0 years (——); Group 2, 25.0–30.0 years (- - - -); Group 3, 30.1–34.9 years (·····); Group 4, ≥ 35.0 years (–·–·).

© 2021 International Society of Ultrasound in Obstetrics and Gynecology.

14690705, 2021, 2, Downloaded from https://obgyn.onlinelibrary.wiley.com/doi/10.1002/uog.23614 by <Shibboleth>-member@kcl.ac.uk, Wiley Online Library on [31/10/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

for log_{10}CO, log_{10}PVR, log_{10}SV, log_{10}MAP and HR, respectively.

Maternal demographic characteristics and medical history

Greater maternal weight at booking was associated with higher log_{10}CO, HR, log_{10}SV and log_{10}MAP, whilst increasing height was associated with higher log_{10}CO and log_{10}SV but lower HR, log_{10}PVR and log_{10}MAP (Table 2). Black and South and East Asian women, compared to white women, had lower log_{10}CO and log_{10}SV but significantly higher log_{10}PVR. Women of black or South Asian racial origin had significantly higher HR than did white women. Parous women, with or without previous PE and/or SGA, compared to nulliparous women, had significantly higher log_{10}CO. Parous women without previous PE and/or SGA had significantly higher HR and lower log_{10}PVR and log_{10}MAP. Women who developed GH had lower log_{10}CO; however, there was no significant contribution of PE or chronic hypertension in the maternal hemodynamic models. There was a significant contribution from the gestational-age window for all the cardiac variables, but interactions between age groups and gestational-age window were not significant. Average cardiac measurements in the four groups at each of the visits, according to whether the pregnancy had a SGA neonate and/or a hypertensive disorder, are presented in Table S1.

Hemodynamic changes over time after controlling for maternal characteristics and outcomes

Log_{10}CO in all four groups increased during the first three visits and declined thereafter, with Group 1 demonstrating greater log_{10}CO throughout gestation, followed by Groups 2, 3 and 4 (Figure 2, Table 3). Log_{10}PVR demonstrated a linear decline in all four groups from Visit 1 to Visit 3, followed by an increase at Visit 4, with Group 4 demonstrating greater log_{10}PVR throughout gestation, followed by Groups 3, 2 and 1. Similar to log_{10}CO, HR in all four groups increased from Visit 1 to Visit 3 but plateaued at the fourth visit. Group 1 demonstrated significantly higher HR, followed by Groups 2, 3 and 4, which is the same order as that observed for log_{10}CO.

DISCUSSION

Main findings

The main findings of this study are, first, maternal CO decreases and PVR increases with increasing maternal age and these differences persist throughout gestation, second, the higher CO in younger women was achieved mainly through an increase in HR without a concomitant rise in SV, third, although the younger age group demonstrated an apparently more favorable hemodynamic profile, they had a higher incidence of a SGA neonate than did older women, and, fourth, there were no significant differences between the age groups in the incidence of PE.

In England, during 2019, the average age of mothers was 30.7 years[28]. Historically, a maternal age of 35 years was considered the cut-off for increased risk of the fetus being affected by trisomy 21[29]. Additionally, fertility declines most dramatically after 35 years of age[30]. This formed the rationale for grouping our study population into quartiles including the national mean and 35 years as a cut-off defining older aged women.

Interpretation of results

Maternal cardiovascular adaptation in normal pregnancy is associated with early vasodilatation leading to a reduction in PVR and a state of vascular underfill. This stimulates a primary increase in HR and a secondary increase in plasma volume of over 50% by the second trimester[31] by retaining about 900 mmol of sodium[32]. Renal adaptation involves an increase in glomerular filtration rate and effective blood flow[31]. Volume-regulating mechanisms, including pregnancy hormones and the renin–angiotensin–aldosterone system, also contribute to the rising plasma volume. Cardiac preload increases during pregnancy and, due to this 'physiological hypervolemia', an increase in SV occurs if the heart has normal diastolic and systolic function. On the contrary, after the late second trimester, a minimal increase in SV occurs, as blood volume remains relatively unchanged and afterload increases[33]. Thereafter, HR becomes the main determinant in offsetting the decrease in cardiac preload and increases throughout pregnancy to maintain optimal CO[34–36]. In our study, all groups demonstrated the expected reduction in PVR and increase in HR, SV and CO during pregnancy.

Outside of pregnancy, increasing age has a negative impact on cardiac function, both at rest and in response to exercise. Age-associated changes in cardiac performance and vascular adaptation to endurance exercise include reduced HR, reduced ejection fraction and blunted vasodilator response, due to a reduction in beta-adrenergic response[20,37–39]. This 'cardiac aging' could be overcome to an extent by chronic physical activity and exercise[40]. However, the decline in left ventricular relaxation and diastolic function cannot be reversed by exercise[41]. Similarly, kidney function decreases by 10% with every decade of increase in age, with younger, compared to older, people having a greater glomerular filtration rate and more effective renal plasma flow[42,43].

To our knowledge, this is the first study to examine the effect of maternal age on longitudinal changes of maternal hemodynamics and fetal growth during pregnancy. Similar to a previous cross-sectional study, we observed decreasing CO and increasing PVR with maternal age, but no change in SV[44]. Although there were differences in CO and PVR between groups, these were modest and not associated with outcome. SV increased with gestation, but there was no difference between groups despite possibly

© 2021 International Society of Ultrasound in Obstetrics and Gynecology.

14690705, 2021, 2, Downloaded from https://obgyn.onlinelibrary.wiley.com/doi/10.1002/uog.23614 by <Shibboleth>-member@kcl.ac.uk, Wiley Online Library on [31/10/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

better intrinsic myocardial function and lower PVR in younger women. It is possible that, in younger women, sodium excretion exceeds retention, causing a depletion in an 'effective circulating volume', as represented by SV[45]. Possible mechanisms include higher sodium loss from the kidneys due to either a higher glomerular filtration rate (as a result of greater vasodilatation and hence lower PVR)[46], or higher progesterone levels, a hormone which triggers an increase in glomerular filtration rate and sodium waste[31,32]. Furthermore, although younger women are expected to have greater SV secondary to better left ventricular filling and contractility, it may be that the heart already operates in the upper flat part of the Frank–Starling curve and, therefore, an increase in preload is accompanied by only a small increase in SV[47]. Indeed, it has been shown that plasma volume expansion beyond 400 mL does not result in any further increase in SV[48]. This suggests that the left ventricle has a limit to its diastolic reserve capacity and end-diastolic dimension.

Groups 1 and 2 had smaller babies. This cannot be explained by maternal hemodynamics, as they had higher CO and lower PVR compared to the other groups. This is in agreement with *in-vitro* fertilization studies reporting that, in women undergoing oocyte donation, despite being older compared to women with natural conception, they have lower uterine artery resistance and no difference in SGA rate[49].

The higher HR and smaller babies in the younger women could be the result of greater use of beta-mimetics or smoking, as we observed that women in Group 1 were nine and two times more likely to be smokers or asthmatic than women in Group 4, respectively.

Although Group 4 had a less favorable hemodynamic profile, reflecting the gradual onset of cardiac and vascular aging[19,29,41,50], their outcomes were not worse than those of younger women. This could be due to the interaction between the greater prevalence of age-related medical conditions, such as chronic hypertension and pre-existing diabetes, as observed in our cohort, and higher socioeconomic status[51,52], leading to better antenatal care and prudent health choices[53,54]. Although smoking and asthma were adjusted for in our model, we cannot be certain of the interplay of medical conditions, lifestyle, nutrition and socioeconomic factors with pregnancy outcome.

Strengths and limitations

Strengths of this study include the large sample size, longitudinal hemodynamic assessment throughout pregnancy and adjustment for variables that may influence hemodynamics. A limitation of our study is the lack of data on socioeconomic status, level of education and health lifestyle of the women. Although our study cohort consists of a general unselected obstetric population in six maternity units across London, the heterogeneous medical and social backgrounds of the younger *vs* older women may balance against each other, accounting for the unexpected similarities in pregnancy outcome across age groups. Furthermore, this study was not powered to address differences in primary maternal outcomes between extreme age groups.

Conclusion

Younger women have the most favorable hemodynamic profile during pregnancy but, despite this, they also have the highest incidence of a SGA neonate.

REFERENCES

1. Hickman LC, Fortin C, Goodman L, Liu X, Flyckt R. Fertility and fertility preservation: knowledge, awareness and attitudes of female graduate students. *Eur J Contracept Reprod Health Care* 2018; **23**: 130–138.
2. Maheshwari A, Porter M, Shetty A, Bhattacharya S. Women's awareness and perceptions of delay in childbearing. *Fertil Steril* 2008; **90**: 1036–1042.
3. Londero AP, Rossetti E, Pittini C, Cagnacci A, Driul L. Maternal age and the risk of adverse pregnancy outcomes: a retrospective cohort study. *BMC Pregnancy Childbirth* 2019; **19**: 261.
4. Gibbs CM, Wendt A, Peters S, Hogue CJ. The impact of early age at first childbirth on maternal and infant health. *Paediatr Perinat Epidemiol* 2012; **26**: 259–284.
5. Chen X-K, Wen SW, Fleming N, Demissie K, Rhoads GG, Walker M. Teenage pregnancy and adverse birth outcomes: a large population based retrospective cohort study. *Int J Epidemiol* 2007; **36**: 368–373.
6. Malabarey OT, Balayla J, Klam SL, Shrim A, Abenhaim HA. Pregnancies in young adolescent mothers: a population-based study on 37 million births. *J Pediatr Adolesc Gynecol* 2012; **25**: 98–102.
7. Huang L, Sauve R, Birkett N, Fergusson D, Van Walraven C. Maternal age and risk of stillbirth: a systematic review. *CMAJ* 2008; **178**: 165–172.
8. Khalil A, Syngelaki A, Maiz N, Zinevich Y, Nicolaides KH. Maternal age and adverse pregnancy outcome: a cohort study. *Ultrasound Obstet Gynecol* 2013; **42**: 634–643.
9. Kenny LC, Lavender T, Mcnamee R, O'Neill SM, Mills T, Khashan AS. Advanced maternal age and adverse pregnancy outcome: evidence from a large contemporary cohort. *PLoS one* 2013; **8**: e56583.
10. Laopaiboon M, Lumbiganon P, Intarut N, Mori R, Ganchimeg T, Vogel J, Souza J, Gülmezoglu A; Network WMSOMNHR. Advanced maternal age and pregnancy outcomes: a multicountry assessment. *BJOG* 2014; **121**: 49–56.
11. Astolfi P, Zonta LA. Delayed maternity and risk at delivery. *Paediatr Perinat Epidemiol* 2002; **16**: 67–72.
12. Stott D, Nzelu O, Nicolaides KH, Kametas NA. Maternal hemodynamics in normal pregnancy and in pregnancy affected by pre-eclampsia. *Ultrasound Obstet Gynecol* 2018; **52**: 359–364.
13. Stott D, Papastefanou I, Paraschiv D, Clark K, Kametas NA. Longitudinal maternal hemodynamics in pregnancies affected by fetal growth restriction. *Ultrasound Obstet Gynecol* 2017; **49**: 761–768.
14. Tay J, Foo L, Masini G, Bennett PR, Mceniery CM, Wilkinson IB, Lees CC. Early and late preeclampsia are characterized by high cardiac output, but in the presence of fetal growth restriction, cardiac output is low: insights from a prospective study. *Am J Obstet Gynecol* 2018; **218**: 517.e1–12.
15. Melchiorre K, Sutherland GR, Liberati M, Thilaganathan B. Maternal cardiovascular impairment in pregnancies complicated by severe fetal growth restriction. *Hypertension* 2012; **60**: 437–443.
16. Melchiorre K, Sutherland G, Sharma R, Nanni M, Thilaganathan B. Mid-gestational maternal cardiovascular profile in preterm and term pre-eclampsia: a prospective study. *BJOG* 2013; **120**: 496–504.
17. Arbab-Zadeh A, Dijk E, Prasad A, Fu Q, Torres P, Zhang R, Thomas JD, Palmer D, Levine BD. Effect of aging and physical activity on left ventricular compliance. *Circulation* 2004; **110**: 1799–1805.
18. Nicholson CJ, Sweeney M, Robson SC, Taggart MJ. Estrogenic vascular effects are diminished by chronological aging. *Sci Rep* 2017; **7**: 12153.
19. El Assar M, Angulo J, Vallejo S, Peiró C, Sánchez-Ferrer CF, Rodríguez-Mañas L. Mechanisms involved in the aging-induced vascular dysfunction. *Front Physiol* 2012; **3**: 132.
20. Lakatta EG, Levy D. Arterial and cardiac aging: major shareholders in cardiovascular disease enterprises: Part I: aging arteries: a "set up" for vascular disease. *Circulation* 2003; **107**: 139–146.
21. Pirhonen J, Bergersen TK, Abdlenoor M, Dubiel M, Gudmundsson S. Effect of maternal age on uterine flow impedance. *J Clin Ultrasound* 2005; **33**: 14–17.
22. Van Der Graaf AM, Zeeman GG, Groen H, Roberts C, Dekker GA. Non-invasive assessment of maternal hemodynamics in early pregnancy. *Pregnancy Hypertens* 2013; **3**: 261–269.
23. Gaillard R, Bakker R, Steegers EA, Hofman A, Jaddoe VW. Maternal age during pregnancy is associated with third trimester blood pressure level: the generation R study. *Am J Hypertens* 2011; **24**: 1046–1053.
24. Robinson HP, Fleming JE. A critical evaluation of sonar "crown-rump length" measurements. *Br J Obstet Gynaecol* 1975; **82**: 702–710.
25. Ling HZ, Gallardo-Arozena M, Company-Calabuig AM, Nicolaides KH, Kametas NA. Clinical validation of bioreactance for the measurement of cardiac output in pregnancy. *Anaesthesia* 2020; **75**: 1307–1313.

© 2021 International Society of Ultrasound in Obstetrics and Gynecology.

14690705, 2021, 2, Downloaded from https://obgyn.onlinelibrary.wiley.com/doi/10.1002/uog.23614 by <Shibboleth>-member@kcl.ac.uk, Wiley Online Library on [31/10/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

26. Nicolaides KH, Wright D, Syngelaki A, Wright A, Akolekar R. Fetal Medicine Foundation fetal and neonatal population weight charts. *Ultrasound Obstet Gynecol* 2018; **52**: 44–51.
27. Brown MA, Lindheimer MD, De Swiet M, Van Assche A, Moutquin JM. The classification and diagnosis of the hypertensive disorders of pregnancy: statement from the International Society for the Study of Hypertension in Pregnancy (ISSHP). *Hypertens Pregnancy* 2001; **20**: IX–XIV.
28. Office for National Statistics. Birth characteristics in England and Wales: 2019. https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/livebirths/bulletins/birthcharacteristicsinenglandandwales/2019#age-of-parents [Accessed 22 January 2021].
29. Cooke CM, Davidge ST. Advanced maternal age and the impact on maternal and offspring cardiovascular health. *Am J Physiol Heart Circ Physiol* 2019; **317**: H387–H394.
30. Johnson JA, Tough S. No-271-Delayed Child-Bearing. *J Obstet Gynaecol Can* 2017; **39**: e500–e515.
31. Brown MA, Gallery ED. Volume homeostasis in normal pregnancy and pre-eclampsia: physiology and clinical implications. *Baillieres Clin Obstet Gynaecol* 1994; **8**: 287–310.
32. Davison JM, Lindheimer MD. Volume homeostasis and osmoregulation in human pregnancy. *Baillieres Clin Endocrinol Metab* 1989; **3**: 451–472.
33. Chapman AB, Abraham WT, Zamudio S, Coffin C, Merouani A, Young D, Johnson A, Osorio F, Goldberg C, Moore LG, Dahms T, Schrier RW. Temporal relationships between hormonal and hemodynamic changes in early human pregnancy. *Kidney Int* 1998; **54**: 2056–2063.
34. Savu O, Jurcut R, Giusca S, Van Mieghem T, Gussi I, Popescu BA, Ginghina C, Rademakers F, Deprest J, Voigt JU. Morphological and functional adaptation of the maternal heart during pregnancy. *Circ Cardiovasc Imaging* 2012; **5**: 289–297.
35. Sanghavi M, Rutherford JD. Cardiovascular physiology of pregnancy. *Circulation* 2014; **130**: 1003–1008.
36. Mahendru AA, Everett TR, Wilkinson IB, Lees CC, Mceniery CM. A longitudinal study of maternal cardiovascular function from preconception to the postpartum period. *J Hypertens* 2014; **32**: 849–856.
37. Stratton JR, Cerqueira MD, Schwartz RS, Levy WC, Veith RC, Kahn SE, Abrass IB. Differences in cardiovascular responses to isoproterenol in relation to age and exercise training in healthy men. *Circulation* 1992; **86**: 504–512.
38. Fleg JL, Schulman S, O'connor F, Becker LC, Gerstenblith G, Clulow JF, Renlund DG, Lakatta EG. Effects of acute beta-adrenergic receptor blockade on age-associated changes in cardiovascular performance during dynamic exercise. *Circulation* 1994; **90**: 2333–2341.
39. Jakovljevic DG. Physical activity and cardiovascular aging: Physiological and molecular insights. *Exp Gerontol* 2018; **109**: 67–74.
40. Goldspink DF. Ageing and activity: their effects on the functional reserve capacities of the heart and vascular smooth and skeletal muscles. *Ergonomics* 2005; **48**: 1334–1351.
41. Prasad A, Popovic ZB, Arbab-Zadeh A, Fu Q, Palmer D, Dijk E, Greenberg NL, Garcia MJ, Thomas JD, Levine BD. The effects of aging and physical activity on Doppler measures of diastolic function. *Am J Cardiol* 2007; **99**: 1629–1636.
42. Miller M. Fluid and electrolyte homeostasis in the elderly: physiological changes of ageing and clinical consequences. *Baillieres Clin Endocrinol Metab* 1997; **11**: 367–387.
43. Fliser D, Ritz E. Renal function and fluid-electrolyte homeostasis changes with age. *Geriatr Nephrol Urol* 1993; **3**: 107–116.
44. Vinayagam D, Thilaganathan B, Stirrup O, Mantovani E, Khalil A. Maternal hemodynamics in normal pregnancy: reference ranges and role of maternal characteristics. *Ultrasound Obstet Gynecol* 2018; **51**: 665–671.
45. Schrier RW, Dürr JA. Pregnancy: an overfill or underfill state. *Am J Kidney Dis* 1987; **9**: 284–289.
46. Davison J. Overview: kidney function in pregnant women. *Am J Kidney Dis* 1987; **9**: 248–252.
47. Mashini IS, Albazzaz SJ, Fadel HE, Abdulla AM, Hadi HA, Harp R, Devoe LD. Serial noninvasive evaluation of cardiovascular hemodynamics during pregnancy. *Am J Obstet Gynecol* 1987; **156**: 1208–1213.
48. Hopper MK, Coggan AR, Coyle EF. Exercise stroke volume relative to plasma-volume expansion. *J Appl Physiol (1985)* 1988; **64**: 404–408.
49. Cavoretto PI, Farina A, Miglio R, Zamagni G, Girardelli S, Vanni VS, Morano D, Spinillo S, Sartor F, Candiani M. Prospective longitudinal cohort study of uterine arteries Doppler in singleton pregnancies obtained by IVF/ICSI with oocyte donation or natural conception. *Hum Reprod* 2020; **35**: 2428–2438.
50. Okada Y, Galbreath MM, Shibata S, Jarvis SS, Vangundy TB, Meier RL, Vongpatanasin W, Levine BD, Fu Q. Relationship between sympathetic baroreflex sensitivity and arterial stiffness in elderly men and women. *Hypertension* 2012; **59**: 98–104.
51. Joseph KS, Liston RM, Dodds L, Dahlgren L, Allen AC. Socioeconomic status and perinatal outcomes in a setting with universal access to essential health care services. *CMAJ* 2007; **177**: 583–590.
52. Mortensen LH, Diderichsen F, Smith GD, Andersen AMN. The social gradient in birthweight at term: quantification of the mediating role of maternal smoking and body mass index. *Hum Reprod* 2009; **24**: 2629–2635.
53. Viau PA, Padula CA, Eddy B. An exploration of health concerns & health-promotion behaviors in pregnant women over age 35. *MCN Am J Matern Child Nurs* 2002; **27**: 328–334.
54. Carolan M. The graying of the obstetric population: implications for the older mother. *J Obstet Gynecol Neonatal Nurs* 2003; **32**: 19–27.

SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Table S1 Differences in cardiac variables in pregnancies with *vs* without a small-for-gestational-age neonate and/or hypertensive disorder in pregnancy, according to maternal age

© 2021 International Society of Ultrasound in Obstetrics and Gynecology.

14690705, 2021, 2, Downloaded from https://obgyn.onlinelibrary.wiley.com/doi/10.1002/uog.23614 by <Shibboleth>-member@kcl.ac.uk, Wiley Online Library on [31/10/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License