CARDIAC MALADAPTATION IN OBESE PREGNANCY AT TERM

Short title: Cardiac Maladaptation in Obese Pregnancy

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ABSTRACT

Objectives: Obesity is an increasing problem worldwide with well-recognized detrimental effects on cardiovascular health. However, very little is known about the effect of obesity on cardiovascular adaptation to pregnancy, as existing studies are small and show conflicting results. The aim of the present study is to compare biventricular cardiac function at term in obese pregnant women and pregnant women of normal body weight utilizing conventional echocardiography indices and speckle tracking assessment.

Methods: For this prospective case control study, 40 obese, but otherwise healthy, pregnant women with a body mass index (BMI) ≥35kg/m^2 and 40 healthy pregnant women with a BMI ≤30kg/m^2 underwent full echocardiography at term.

Results: Obese pregnant women had significantly higher systolic blood pressure (117 vs. 109mmHg, p=0.002), cardiac output (6.73 vs. 4.89L/min, p<0.001), left ventricular mass index (74 vs. 64g/m^2, p<0.001) and relative wall thickness (0.43 vs. 0.37, p<0.001). Diastolic dysfunction was present in 12.5% (n=5) of controls and 41% (n=16) of obese women (p=0.004). Left ventricular global longitudinal strain (-15.59 vs. -17.61%, p<0.001), left ventricular endocardial (-17.30 vs. -19.84±%, p<0.001) and epicardial (-13.10 vs. -15.73%, p<0.001) global longitudinal strain as well as left ventricular early diastolic strain rate (1.05 vs. 1.24s^{-1}, p=0.006) were all significantly reduced in the obese group. No differences were observed in left ventricular twist and torsion.

Conclusion: These findings are likely to represent a maladaptive response of the heart to volume overload in pregnancy. The impact of theses changes on pregnancy outcome and long-term maternal outcome is unclear.

INTRODUCTION

Obesity and being overweight are worldwide epidemics in low-, middle and high-income countries alike. According to the World Health Organization, 39% of all adults were considered overweight (BMI ≥ 25kg/m^2) and 13% were considered obese (BMI ≥ 30kg/m^2) in 2016. [1-3] The adverse effects of obesity on cardiovascular health are well-recognized. [4-9] Obesity is associated with an increase in circulating blood volume, stroke volume, systemic and pulmonary arterial pressure – predisposing to biventricular hypertrophy as well as left atrial enlargement. At a functional level, both left ventricular systolic and diastolic function can be impaired, and in severe cases, obesity can even lead to right ventricular failure. [9, 10] In pregnancy, obesity is associated with a number of adverse consequences such as spontaneous pregnancy loss, gestational diabetes, fetal growth restriction, preeclampsia, higher risk of caesarean delivery and increased risk of venous thromboembolism. [11-13] Very little data however exists on how obesity affects the cardiovascular system of expectant mothers. Existing studies are small and include only conventional echocardiography measurements or less reliable, non-invasive cardiovascular output monitoring. [14-18]

Pregnancy is a state of chronic volume overload. Echocardiography studies have shown that even a small proportion of healthy pregnant women show signs of cardiac maladaptation to volume overload at term. [19] We hypothesize that echocardiographic signs of chronic volume overload are more pronounced in obese pregnancy, because volume and resistance load associated with pregnancy are added to the pre-existing volume overload of obesity. New echocardiography technologies such as speckle tracking are more sensitive in detecting subclinical myocardial changes than

conventional echocardiography. [20, 21] There is a paucity of data using speckle-tracking imaging to evaluate cardiac strain and ventricular torsion in obese pregnancy. The aim of the present study is to use speckle-tracking imaging to compare biventricular cardiac function in morbidly obese and normal weight pregnant women at term.

METHODS

This prospective case-control study was carried out at St. George's University Hospitals NHS Foundation Trust in London over a 12-month period from April 2016 until March 2017. The local institutional review committee approved the study (ID 12/LO/0810) and all participants provided written informed consent. We recruited pregnant women at term with a body mass index (BMI) of 35kg/m^2 or more at booking. Only women without any cardiovascular co-morbidities or any form of diabetes (type I, type II or gestational diabetes) and who did not take any cardiovascular medication were asked to take part in the study. Healthy term pregnant women with a BMI of 30kg/m^2 or less at booking and without any co-morbidity were recruited as controls. For both cases and controls, only women with a singleton pregnancy without pregnancy complications (such as preeclampsia or fetal growth restriction) were considered. Blood pressure was measured manually from the brachial artery according to the guidelines of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy.[22] A blood pressure cuff with the appropriate size for the diameter of the upper arm of the participants was used.

Echocardiography

Echocardiography examination and analysis were performed by a single operator (BSB) using a GE Vivid Q® ultrasound machine equipped with a 3.5-MHz transducer. Images were acquired at rest in the left lateral decubitus position from standard parasternal and apical views. Digital loops of 3 cardiac cycles with associated electrocardiogram

information were stored on the hard disk of the ultrasound machine and transferred to a GE EchoPac® workstation for offline analysis. Analysis was performed according to existing guidelines. [23-25] Ventricular wall and chamber dimensions were measured in the parasternal long axis view. Left atrial volume (LAV) and left ventricular volume in diastole (LVEDV) were calculated from apical views. Right atrial area, right ventricular basal and mid cavity diameter and right ventricular longitudinal diameter were measured from apical views. Proximal and distal right ventricular outflow tract (prox. and dist. RVOT) were measured in parasternal short axis views. TAPSE was measured from apical M-Mode images. Right ventricular fractional area change was calculated from apical views. Doppler images were used to measure early and late mitral and tricuspid valve inflow velocities (E and A, RV E and RV A), mitral and tricuspid inflow deceleration time (DT, RV DT), isovolumetric relaxation time (IVRT), systolic and diastolic flow in the pulmonary veins, duration of the late mitral valve inflow (A dur), duration of the flow in the pulmonary vein during atrial contraction (AR dur) and acceleration time of the flow through the pulmonary valve (PV acc. time). Tissue Doppler images were used to measure systolic (S'), early diastolic (E') and late diastolic (A') tissue velocities at the septal and lateral mitral valve and at the right ventricular free wall. Left ventricular mass was calculated using the Devereux formula $0.8(1.04[([LVEDD + IVSd + PWd]^3 - LVEDD^3)]) + 0.6v$, where LVEDD is left ventricular end diastolic diameter, IVSd is thickness of the intraventricular septum in diastole and PWd is posterior wall thickness in diastole. Relative wall thickness was calculated with the formula (2*PWd)/LVEDD. Total vascular resistance was (TVR) was calculated with the formula 80*MAP/(CO/1000), where MAP is mean arterial pressure and CO cardiac

output. Diastolic dysfunction was classified according to the guidelines of the British Society of echocardiography applying the age and gender adapted values from the 2016 European Society of Cardiology Guidelines for the diagnosis and treatment of acute and chronic heart failure.[26, 27]

Speckle tracking echocardiography

The myocardium was traced manually and EchoPac® software used to identify an area of interest by delimiting the endocardium and epicardium. The operator readjusted this area before the software calculated deformation. LV and RV global longitudinal strain and strain rate were calculated from apical views, with negative values indicating fiber shortening. LV rotation and de-rotation were calculated from apical and basal parasternal short axis views, with negative values indicating rotation in the clockwise direction. LV twist is the difference between the apical and the basal rotation, LV torsion is LV twist divided by left ventricular length in diastole. If >1 segment was rejected, subjects were excluded from statistical analysis.

Statistical analysis

Descriptive statistics were performed. Continuous data were presented as mean (standard deviation, SD). Normal distribution was assessed using Shapiro-Wilk test. Categorical data were presented as number (%) and were compared using the Chi square test. Comparisons between the groups were performed using either unpaired t-

test or Mann Whitney U test for continuous data, depending on distribution of data.

IBM SPSS statistics version 24 was used.

RESULTS

We enrolled a total of 80 pregnant women at term, 40 obese, but otherwise healthy, women and 40 healthy women of normal weight. Conventional echocardiography evaluation of the left ventricle could be performed in all women, but right ventricular images could not be obtained in three controls and eight obese women. Speckle-tracking analysis could not be performed in seven women (5 controls and 2 obese) in the left ventricle.

Demographic characteristics of the control and obese groups are shown in Table 1. Obese women had significantly higher systolic and diastolic blood pressure at booking, but only significantly higher systolic blood pressure at term. Heart rate and cardiac output (CO) were significantly higher in the obese group compared to controls. Stroke volumes (SV) were comparable between the two groups and the total vascular resistance (TVR) was significantly lower in the obese group. Differences in cardiac output and total vascular resistance were no longer significant when indexed to body surface area (CI and TVRI). Obese individuals had a significantly higher left ventricular mass (LVM), left ventricular mass index (LVMI) and relative wall thickness (RWT).

Diastolic dysfunction was present in 12.5% of controls (four grade I and one grade II) and 41% of obese women (14 grade I and two grade II; Table 2). Speckle tracking analysis demonstrated significantly lower LV (endocardial and epicardial) global longitudinal strain, and LV early diastolic strain rate. No differences were observed in left ventricular twist and torsion mechanics (Table 2). Right ventricular measurements showed a significantly larger distal RV outflow tract and decreased E/A ratio in obese women (Table 3; Figure 1).

DISCUSSION

Obese pregnant women at term demonstrated significantly higher heart rate, cardiac output and LV mass compared to normal weight term pregnant women. Conventional and speckle-tracking echocardiography assessment demonstrated significantly reduced LV global longitudinal strain and increased prevalence of diastolic dysfunction in obese women compared to controls. These subclinical changes suggest a significantly maladaptive cardiovascular response in apparently uncomplicated term pregnancy in obese women.

Previous studies on cardiac function in obese pregnancy included fewer women, only used conventional echocardiography and focused solely on left ventricular changes. [14-16] To our knowledge this is the first study looking comprehensively at biventricular function and utilizing speckle-tracking assessment. Obesity in pregnancy is a strong risk factor for the development of hypertensive disorders of pregnancy, fetal growth restriction and gestational diabetes – all pregnancy pathologies where recent work has shown significant deficits in maternal cardiovascular function.[28-33] By deliberately excluding obese women who developed these complications from our prospective study, we may have inadvertently introduced exclusion bias by not studying obese women who developed cardiac dysfunction as a consequence of these pregnancy complications. Hence, our data is more reflective of the cardiac function in apparently 'healthy' obese women rather than showing the evolution of more severe cardiac dysfunction as has been shown to occur with the development of preeclampsia or fetal growth restriction.[34-37] Despite these exclusions, it is notable that the prevalence of

diastolic dysfunction is almost three-fold higher in obese compared to normal pregnancy at term.[19] The latter observation has previously been implicated in the development of hypertensive disorders of pregnancy.[19, 38, 39]

Comparison with previous work

There are a number of studies focusing on subclinical myocardial dysfunction in young healthy obese non-pregnant individuals. Share *et al.* studied healthy women aged 18-30 years with abdominal obesity and compared them to non-obese controls,[40] whilst others assessed obese children and adolescents or metabolically healthy young adults.[41, 42] These studies all reported that cardiac function assessed by conventional echocardiography was similar between the obese and non-obese groups. However, speckle tracking strain measurements revealed subclinical myocardial impairment in all of the studies. Previous echocardiography studies on obesity in pregnancy reported similar geometrical changes as we observed.[14-16] The findings of the current study support the hypothesis that the volume and pressure load associated with pregnancy causes significant cardiac maladaptation in obese pregnant women at term.

Study limitations and strengths

Obese women were scanned two weeks earlier and were younger than normal weight controls. Previous work showed that maladaptation to the chronic volume overload of pregnancy increases towards term.[19] If the difference in the gestational age at the time of echocardiography had an impact on the result, it would have acted to ameliorate

any potential differences between the obese and the normal weight groups – as would the effect of maternal age.

Conclusion

Morbidly obese, but otherwise apparently healthy, pregnant women at term had significant LV hypertrophy with evidence of diastolic dysfunction and impaired deformation indices. These changes represent a maladaptive response to pregnancy and may explain the increased prevalence of adverse pregnancy outcomes related to uteroplacental dysfunction observed in obese pregnant women. We can however not exclude the possibility that some of these deficits were already present prior to pregnancy.

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DECLARATION OF INTEREST

None

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FIGURE LEGENDS

Figure 1: Representative speckle tracking and strain rate analysis for A) left ventricular apical 4-chamber and B) right ventricle.

TABLES

Table 1: Demographic characteristics of obese (n=40) and control subjects (n=40)			
	Normotensive Controls (n=40)	**Obese (n=40)**	**p-value**
Maternal age (years)	34.80 (4.03)	31.70 (5.22)	0.004
Ethnicity:			0.004
- Caucasian	34 (85.0%)	26 (65.0%)	
- Afro-Caribbean	2 (5.0%)	13 (32.5%)	
- Asian	4 (10.0%)	1 (2.5%)	
Parity:			0.651
- Nulliparous	16 (40.0%)	18 (45.0%)	
- Multiparous	24 (60.0%)	22 (55.0%)	
Booking BMI (kg/m^2)	23.70 (2.47)	41.43 (6.65)	<0.001
SBP at booking visit (mmHg)	109 (11)	122 (10)	<0.001
DBP at booking visit (mmHg)	67 (8)	75 (7)	<0.001
BMI at assessment (kg/m^2)	28.14 (2.96)	44.32 (7.27)	<0.001
Gestational age at assessment (weeks)	39.31 (1.02)	36.88 (1.33)	<0.001
SBP at assessment (mmHg)	109 (9)	117 (11)	0.002
DBP at assessment (mmHg)	74 (8)	76 (8)	0.234
Results are shown as mean (±SD) or number of subjects (percentage). p<0.05 considered significant and p<0.001 highly significant. BMI=body mass index; SBP=systolic blood pressure; DBP=diastolic blood pressure			

Table 2: Left ventricular hemodynamic, geometric and speckle tracking-derived indices of obese (n=40) and control (n=40) subjects.

	Normotensive Controls (n=40)	**Obese (n=40)**	**p-value**
Hemodynamic Indices			
HR (min^{-1})	75 (9)	90 (12)	**<0.001**
SV (ml)	66 (11)	75 (17)	0.008
SVI ($ml*m^{-2}$)	36 (6)	33 (7)	0.107
CO ($ml*min^{-1}$)	4896 (849)	6725 (1869)	**<0.001**
CI ($ml*min*m^{-2}$)	2664 (439)	3012 (747)	0.013
TVR ($dynes*s^{-1}*cm^{-5}$)	1448 (332)	1163 (411)	**<0.001**
TVRI ($dynes*s^{-1}*cm^{-5}*m^{-2}$)	2658 (605)	2563 (848)	0.567
Average S' (m/s)	0.10 (0.02)	0.10 (0.02)	0.961
Geometric Indices			
LAV (ml)	55 (12)	64 (18)	0.013
LAVI ($ml*m^{-2}$)	30 (6)	29 (7)	0.405
LVM (g)	119 (21)	164 (30)	**<0.001**
LVMI ($g*m^{-2}$)	64 (10)	74 (12)	**<0.001**
RWT	0.37 (0.08)	0.43 (0.05)	**<0.001**
Mitral inflow indices			
E (m/s)	0.73 (0.12)	0.73 (0.13)	0.991
A (m/s)	0.57 (0.11)	0.65 (0.11)	0.005
E/A ratio	1.28 (0.18)	1.16 (0.31)	0.033
Septal E' (m/s)	0.10 (0.03)	0.10 (0.02)	0.354
Lateral E' (m/s)	0.15 (0.04)	0.14 (0.03)	0.873
E/E' average	6.18 (1.57)	6.15 (1.25)	0.933

Diastolic Function **- Normal** **- Grade 1 Diastolic Dysfunction** **- Grade 2 Diastolic Dysfunction** **- Grade 3 Diastolic Dysfunction**	 35 (87.5) 4 (10) 1 (2.5) 0 (0)	 23 (59) 14 (35.9) 2 (5.1) 0 (0)	0.004
Strain and strain rate indices			
LV Global Longitudinal Strain (%)	-17.61 (1.89)	-15.59 (2.46)	**<0.001**
LV Endocardial Global Longitudinal strain (%)	-19.84 (2.35)	-17.30 (2.85)	**<0.001**
LV Epicardial Global Longitudinal Strain (%)	-15.73 (1.66)	-13.10 (2.01)	**<0.001**
LV Longitudinal Strain Rate (s^{-1})	-0.98 (0.12)	-0.95 (0.20)	0.362
LV Early Diastolic Strain Rate (s^{-1})	1.24 (0.26)	1.05 (0.32)	0.006
LV Late Diastolic Strain Rate (s^{-1})	0.55 (0.16)	0.60 (0.26)	0.361
Twist and torsion indices			
LV Twist (degree)	14.33 (5.69)	17.67 (7.48)	0.064
LV Torsion (degree*cm^{-1})	1.66 (0.66)	1.94 (0.87)	0.187
LV Twist Rate (degree*s^{-1})	102 (48)	134 (57)	0.061
LV Un-Twist Rate (degree*s^{-1})	-106 (56)	-133 (64)	0.105

Results are shown as mean (±SD). $p<0.05$ considered significant and $p<0.001$ highly significant.

BSA=body surface area; HR=heart rate; MAP=mean arterial pressure; SV=stroke volume; SVI=stroke volume index; CO=cardiac output; CI=cardiac index; TVR=total vascular resistance; TVRI=total vascular resistance index; Average S'=systolic tissue Doppler average velocity at the septal/lateral mitral valve annulus; LAV=left atrial volume; LAVI=left atrial volume index; LVM=left ventricular mass; LVMI=left ventricular mass index; RWT=relative wall thickness; E=peak early diastolic transmitral valve velocity; A=peak late diastolic transmitral valve velocity; Septal/lateral E'=peak early diastolic tissue Doppler velocity at the septal/lateral mitral valve annulus; E/E' average=E to average lateral and septal E' ratio

Table 3: Right Heart Geometry and Function of obese (n=40) and control subjects (n=40)

	Normotensive Controls (n=40)	**Preeclampsia (n=30)**	**p-value**
RAA (cm^2)	14.6 (2.3)	18.9 (12.44)	0.039
Prox. RVOT (cm)	2.79 (0.40)	3.04 (0.44)	0.012
Dist. RVOT (cm)	2.43 (0.27)	2.66 (0.27)	**<0.001**
RV FAC (%)	42 (5)	38 (7)	0.016
TAPSE (cm)	2.27 (0.40)	2.22 (0.37)	0.600
RV S'	0.14 (0.02)	0.16 (0.03)	0.013
PV acc. time (ms)	66 (11)	59 (8)	0.002
RV E (m/s)	0.48 (0.08)	0.49 (0.09)	0.536
RV A (m/s)	0.39 (0.08)	0.50 (0.11)	**<0.001**
RV E/A ratio	1.29 (0.35)	1.02 (0.24)	**<0.001**
RV DT	219 (52)	192 (40)	0.025
RV E'	0.13 (0.04)	0.12 (0.04)	0.353
RV A'	0.14 (0.05)	0.15 (0.05)	0.394
Strain and strain rate analysis			
RV Global Longitudinal Strain (%)	-19.86 (4.62)	-16.70 (4.80)	0.017
RV Endocardial Global Longitudinal Strain (%)	-23.33 (4.77)	-19.86 (5.67)	0.017
RV Epicardial Global Longitudinal Strain (%)	-17.06 (4.43)	-14.40 (4.22)	0.030
RV Longitudinal Strain Rate (s^{-1})	-1.16 (0.26)	-1.05 (0.32)	0.170
RV Early Diastolic Strain Rate (s^{-1})	1.15 (0.28)	0.90 (0.39)	0.009
RV Late Diastolic Strain Rate (s^{-1})	0.69 (0.30)	0.77 (0.29)	0.321

Results are shown as mean (±SD). $p<0.05$ considered significant and $p<0.001$ highly significant.

RAA=right atrial area; RVD 1=right ventricular basal diameter; RVD 2=right ventricular mid cavity

diameter; RVD 3=right ventricular longitudinal diameter; Prox. RVOT=diameter of the proximal right ventricular outflow tract; dist RVOT=diameter of the distal right ventricular outflow tract; RV FAC=right ventricular fractional area change; TAPSE=tricuspid annular plane systolic excursion; RV S'=peak systolic tissue Doppler velocity at the tricuspid valve annulus; PV acc. Time=pulmonary valve acceleration time; RV E=peak early diastolic trans-tricuspid valve velocity; RV A=peak late diastolic trans-tricuspid valve velocity; RV DT=deceleration time of RV E wave; RV E'=peak early diastolic tissue Doppler velocity at the tricuspid valve annulus