Maternal cardiovascular adaptation to pregnancy in obese pregnant women: an observational longitudinal study

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Abstract

Objective Obesity is known to be associated with cardiovascular compromise and is a major risk factor for the development of hypertensive disorders in pregnancy. The aim of this study was to investigate the effect of obesity on the maternal cardiovascular system. Design This was a prospective, observational, longitudinal study. Setting A tertiary centre in London Population Pregnant women with booking body mass index (BMI) [?] 30kg/m2 (n=64) were compared to pregnant women with normal booking BMI (20-24.9kg/m2) (n=14). Methods Two-dimensional trans-thoracic echocardiography. Main outcomes Longitudinal difference in blood pressure, cardiac geometry and cardiac function between the groups. Results In women with obesity, the blood pressure, heart rate and cardiac output were higher and peripheral vascular resistance was lower ($p<0.01$ for all) compared to normal BMI women. Women with obesity had altered cardiac geometry with higher left ventricular end diastolic diameter, relative wall thickness and left ventricular mass ($p<0.001$ for all comparisons). There was also evidence of impaired diastolic indices in the obese group with lower E/A ratio, TDI E' lateral and medial and higher left atrial volume ($p<0.01$ for all). Finally, women with obesity had reduced longitudinal function between the second and third trimester of pregnancy indicating possible early cardiac dysfunction in this group. Conclusions Obesity is associated with maternal hyperdynamic circulation, altered cardiac geometry and suboptimal diastolic function compared to normal BMI pregnant women; this may contribute to the increased risk of complications in obese pregnant women. Funding UK charities: Borne and CW+

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Objective

Obesity is known to be associated with cardiovascular compromise and is a major risk factor for the development of hypertensive disorders in pregnancy. The aim of this study was to investigate the effect of obesity on the maternal cardiovascular system.

Design

This was a prospective, observational, longitudinal study.

Setting

A tertiary centre in London

Population

Pregnant women with booking body mass index (BMI) [?] 30kg/m2 (n=64) were compared to pregnant women with normal booking BMI (20-24.9kg/m2) (n=14).

Methods

Two-dimensional trans-thoracic echocardiography.

Main outcomes

Longitudinal difference in blood pressure, cardiac geometry and cardiac function between the groups.

Results

In women with obesity, the blood pressure, heart rate and cardiac output were higher and peripheral vascular resistance was lower ($p<0.01$ for all) compared to normal BMI women. Women with obesity had altered cardiac geometry with higher left ventricular end diastolic diameter, relative wall thickness and left ventricular mass ($p<0.001$ for all comparisons). There was also evidence of impaired diastolic indices in the obese group with lower E/A ratio, TDI E' lateral and medial and higher left atrial volume ($p<0.01$ for all). Finally, women with obesity had reduced longitudinal function between the second and third trimester of pregnancy indicating possible early cardiac dysfunction in this group.

Conclusions

Obesity is associated with maternal hyperdynamic circulation, altered cardiac geometry and suboptimal diastolic function compared to normal BMI pregnant women; this may contribute to the increased risk of complications in obese pregnant women.

Funding

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Introduction

Obesity has nearly tripled since 1975 and the World Health Organisation estimate that in 2016, 650 million adults (13%) had obesity.[1] In the UK, this epidemic is perpetuated and in 2020, 60% of women were overweight and 29% obese. Many of these woman are of childbearing age and go on to have high risk pregnancies.[2] Obesity outside pregnancy has several effects on the cardiovascular system as every 100g of

fat deposited increases the cardiac output (CO) by 30–50 ml/minute and this high volume load can lead to left ventricle (LV) dilation with subsequent hypertrophy, impaired LV relaxation and compliance resulting in diastolic dysfunction. [3, 4] Furthermore, conduction and contractility can be compromised when fat deposition occurs in the myocardial tissue and in severe sustained obesity, systolic dysfunction can also ensue. [5, 6]

Normal pregnancy is associated with significant maternal cardiovascular and haemodynamic changes that are needed to support fetal growth, with systemic vasodilation leading to reduced peripheral vascular resistance and increased stroke volume (SV) and CO. [7] In addition, there is physiological eccentric cardiac remodelling with increased LV mass and reduced diastolic reserve with evidence of dysfunction in around 25% of women at term. [8] Obesity in pregnancy is associated with an increased risk of hypertensive disorders, gestational diabetes (GDM), venous thromboembolism, dysfunctional/prolonged labour, caesarean section and even, mortality.[9] In particular, booking BMI>35 kg/m^2 doubles the risk of pre-eclampsia (PE) and there is a dose dependent relationship with morbidly obese women having the highest incidence; around five-fold higher than normal BMI women.[10, 11] Pre-eclampsia has been associated with maternal cardiovascular compromise and echocardiographic studies have demonstrated significant cardiac dysfunction both in the pre-clinical and clinical phase of the disease. [12, 13] However, studies of the effect of obesity on the maternal cardiovascular system are limited. A cross-sectional study at term (n=40) found that morbidly obese pregnant women (BMI[?]35 kg/m^2) had higher CO, lower resistance, altered geometry and a degree of diastolic and systolic dysfunction , compared to pregnant women with BMI<30kg/m^2. [14] The only longitudinal study (n= 232) has demonstrated that women with obesity start in a state of high volume/low resistance which gradually moves to volume overload with decreased CO and disappearance of low vascular resistance in the third trimester. However, this study assessed haemodynamic function using impedance cardiography and therefore did not examine the maternal cardiac geometry or function. [15]The aim of the current study was to provide novel longitudinal data of the maternal cardiovascular profile (including haemodynamic function, cardiovascular geometry and systolic and diastolic function) in obese pregnant women, compared to women with normal BMI, using a two dimensional echocardiography which is considered the gold standard.[16] We hypothesised that the women with obesity will have a suboptimal cardiovascular profile.

Methods

This was a prospective, observational, longitudinal study conducted in an inner London Hospital between April 2018 to June 2020. Pregnant women without significant co-morbidities, including chronic hypertension or kidney disease, with a singleton pregnancy were recruited soon after their first trimester scan and seen at three time points during pregnancy; 12-14, 20-24 and 30-32 weeks of gestation. Participants were allocated to the following groups: Group 1 – Pregnant women with BMI [?]30kg/m^2 and Group 2 – Pregnant women with BMI 20-24.9kg/m^2. The study protocol has been described before and none of the participants had a history of bariatric surgery.[17] All participants gave a written consent form and the study was approved by the National Health Service Research Ethics Committee (No: 14/LO/0592). Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines were used throughout.

Blood pressure (BP) measurements were performed twice, electronically (Microlife WatchBP, Switzerland),[18] and mean arterial pressure (MAP) was calculated as Systolic BP + (2 x Diastolic BP)]/3.[19] The maternal cardiac function was assessed using transthoracic echocardiography and two-dimensional, M-mode and tissue Doppler imaging (TDI) were used (iE33 Philips Ultrasound system) according to European and American guidelines. [20, 21]All echocardiographic studies were performed by experienced operators (DP and NB).

Cardiac output (ml or L/min) was calculated as stroke volume (SV) x heart rate (HR). [22] Stroke volume (ml) was calculated as the cross-sectional area of the left ventricular outflow tract x velocity time integral. [22] Peripheral vascular resistance (dynes/sec/ per cm^5) was calculated as MAP $\times$ 80/CO. [19, 23] Left ventricular mass (g) was calculated as (0.8 x (1.04x [(interventricular septum diameter (mm) + left ventricle internal diameter (mm) + posterior wall thickness (mm))$^{3)}$ - left ventricle internal diameter^3 (mm)]) + 0.6g. [20]Relative wall thickness was calculated as (2 x posterior wall thickness (mm)) / left ventricle internal diameter (mm).

All measurements were taken in diastole. Body surface area (BSA) was calculated as (weight (kg)$^{0.425}$ x height (cm)$^{0.725}$) x 0.007184. [24] Haemodynamic function was assessed by systolic BP, diastolic BP, HR, SV, CO and PVR. Cardiac geometry was assessed by left atrial (LA) diameter (end-systole), interventricular septum thickness (IVS) (end-diastole), left ventricle diameter (LVEDD) (end-diastole), posterior wall thickness (PWT) (end-diastole), relative wall thickness (RWT) and left ventricular mass. Diastolic function was assessed by mitral flow velocity (E/A ratio), TDI lateral and medial mitral annular velocity (E') and left atrial volume. Systolic function was assessed by end-diastolic volume, end-systolic volume, ejection fraction and TDI s' at the lateral tricuspid annulus. Longitudinal function was assessed by mitral annular plane systolic excursion (MAPSE) at the septal and lateral annulus. All echocardiographic data were stored for offline analysis, which was performed by experienced operators (DP and NB) who were blinded to the allocation of the study participants. We have previously shown that the inter- and intra-observer variability in our Unit is >0.8, indicating good reliability. [17]

Women were followed up in pregnancy and all of them underwent a full oral glucose tolerance test at 28-30 weeks of gestation. Gestational diabetes was defined according to the National Institute of Health and Care Excellence (NICE) guidelines of fasting plasma glucose level [?]5.6 mmol/L and/or a 2-hour plasma glucose level [?]7.8 mmol/L.[25] Information on pregnancy outcomes were obtained from the Hospital's perinatal database. Birthweight (BW) was recorded at birth and BW percentiles were calculated. [26]Hypertension was defined as persistent maternal BP [?]140/90 mmHg and pre-eclampsia was defined as hypertension with significant proteinuria.[27]

Statistical analyses

Normality of the data was assessed by the Kolmogoroff–Smirnoff test and data were expressed as mean (standard deviation) and median (interquartile range) for normally and non-normally distributed data, respectively. Categorical variables were expressed as number (percentage). The groups were compared using the unpaired Student t-test/Mann-Whitney or chi-square (χ^2) for numerical and categorical data, respectively.

Logarithmic transformation was performed for non-parametric data and multilevel linear mixed-effects models were used to compare the groups. The fixed effect component included time (the three study visits), study group, maternal age, race, smoking, gestational age at the time of echocardiography, development of GDM and first-order interaction between time and study group. A higher numbers of cases compared to controls were chosen in order to produce more precise effect measures, also considering that echocardiographic data of pregnant women with normal BMI has been previously reported; [8] our sample size reflected a paucity of data in obese pregnant women. Considering a 4:1 ratio for cases and controls, our study had >80% power (at alpha=0.05) to detect an 1829ml/min difference in CO, 0.12 difference in E/A ratio and 65g difference in LV mass between groups.[14] Statistical analyses were performed using International Business Machines (IBM) Statistical Package for the Social Sciences (SPSS) for Windows 2019, version 26.0, IBM Corp., Armonk, New York, USA. Differences were considered statistically significant at $p<0.05$.

Results

We approached 105 pregnant women (n=85 with BMI[?]30kg/m^2 and n=20 with BMI 20-25kg/m^2) and of those, 70 obese and 16 normal BMI women agreed to take part. Those who attended at least two out of the three research visits, with known pregnancy outcome, were included in the study which comprised 64 women with BMI[?]30kg/m^2 and 14 women with normal BMI. All women delivered a live, phenotypically normal neonate. The maternal characteristics and pregnancy outcomes of the study population are given in Table 1. There were no significant differences in the maternal demographic characteristics between the study groups except for maternal booking BMI, as expected.

Haemodynamic function

Compared to the normal BMI group, women with obesity had higher systolic BP, diastolic BP and HR in each trimester and in the overall analysis. Similarly, CO and SV were higher and PVR lower in the obese compared to the normal BMI group, in each trimester and overall (Table 2, Table S1 and Figure 1). SV and CO trended up in both groups with a significant increase in CO from the first to the third trimester (Table S2).

Cardiac Geometry

Overall and in each trimester the LA diameter, IVS, LVEDD, PWT, RWT, LV mass and LV mass index were all higher in the obese compared to the normal BMI group (Table 2, Table S1 and Figure 1). The prevalence of concentric LV hypertrophy (RWT>0.42 and LV mass index >95g/m^2) was higher in the obese women in all trimesters (Table 2).

Systolic, diastolic and longitudinal function

There was no difference in EDV index, ESV index or ejection fraction between the groups (Table 3 and Table S1). E/A ratio and TDI E' lateral reduced with gestation in both groups (Table S2) and women with obesity had lower E/A ratio, TDI E' at the lateral and medial annulus and higher E/E' ratio (Table 3, Table S1 and Figure 2), suggesting worse diastolic function, compared to normal BMI women. Longitudinal function of the right heart, assessed by tricuspid annular plane systolic excursion (TAPSE), was lower in women with obesity (Table 3 and Table S1). Left longitudinal function, assessed by mitral annular plane systolic excursion (MAPSE) at the lateral and septal annulus, reduced with gestation in the obese but not in the normal BMI group (Table S2) although there was no significant difference between the groups.

Discussion

We have shown that, obese pregnant women have a different haemodynamic profile, altered cardiac geometry and impaired diastolic indices compared to pregnant women with normal BMI. This is the first study to present longitudinal data of cardiac function using 2D echocardiography in obese pregnant women. In particular, we found that women with obesity have higher SBP, DBP, HR, SV and CO with lower PVR. They also demonstrate higher PWT, RWT, LV mass and LV mass index with impaired diastolic indices including lower E/A ratio, TDI E' lateral, TDI E' medial and higher E/E' ratio suggesting, suboptimal cardiac geometry, haemodynamic and diastolic function. In addition, we have a novel finding of a reduction in MAPSE between the second and third trimester in the obese group and lower TAPSE in this group compared to the normal BMI pregnant women, indicating possible impaired function in pregnant women with obesity.

Our haemodynamic findings in the obese group are consistent with literature of non-pregnant obese individuals. [5]Obesity is associated with increased plasma volume expansion and CO due to excess body mass, with a concomitant decrease in natriuresis.[28] The raised CO leads to glomerular hyperfiltration and in turn raised distal tubular sodium delivery. [28]Complex mechanisms lead to the upregulation of the renin-aldosterone-angiotensin system and stimulation of the sympathetic nervous system, which can result in increased sodium reabsorption, plasma volume expansion and arterial hypertension. [28, 29] Heart rate is known to be raised in obese individuals due to autonomic impairment, defined by a reduction in parasympathetic activity and relative predominance of the sympathetic nervous system.[5, 30] Maternal PVR decreased with gestation in both groups, in accordance with normal pregnancy physiology as peripheral vasodilation leads to a fall in systemic vascular resistance[7], and was lower in the obese, compared to the normal BMI group. Obese individuals have an expanded intravascular volume to meet the elevated metabolic requirements and as PVR is proportional to MAP and CO, an elevated CO, seen in our obese group, will result in PVR reduction. [31, 32]

We found a significant increase in LV mass and RWT across gestation in both groups, probably due to physiological myocardial hypertrophy needed to support the increased CO in pregnancy.[8, 33]Maternal LA diameter, IVS, LVEDD, PWT, RWT, LV mass, LV mass index and LV hypertrophy prevalence were all significantly higher in the obese group. Pregnancy itself is a hyperdynamic state and even in normal pregnancy a small proportion of "healthy" pregnant women (5-6%) will have LV hypertrophy, defined by LV mass index>95g/m^2 and RWT>0.42.[8] Here we report that obese pregnant women have an even more marked hyperdynamic circulation, probably, in order to cope with the metabolic demands of increased adipose tissue and fat-free mass, which can lead to LV dilation, increased wall stress and compensatory LV hypertrophy. Furthermore, hyperinsulinemia and hyperleptinaemia, seen in obese individuals, could also be involved in the pathogenesis of LV hypertrophy seen in this population.[5, 34, 35]

With regard to cardiac function, we found a reduction in diastolic indices, including E/A ratio and TDI E' at the lateral mitral annulus, with gestation in both groups. [8] It is conceivable that the physiological maternal myocardial hypertrophy reduces LV compliance, leading to a reduction in early diastolic filling and a greater need for atrial contraction which can result in an increased A-wave and reduced E/A ratio. [8, 36] When comparing the groups, the E/A ratio and TDI E' lateral and medial were higher and E/E' ratio lower in the obese group. [37, 38] Obesity associated LV hypertrophy leads to impaired relaxation and early filling abnormalities which are compensated by augmented atrial contribution; these findings represent an early index of cardiac dysfunction even when systolic performance is maintained. [39] We found no difference in ejection fraction between groups, which is consistent with obese individuals outside pregnancy. [5, 40] Mitral annular plane systolic excursion assesses longitudinal function and gives an indication of systolic function [41] and in normal pregnancy, lateral and septal MAPSE have been reported to be reduced at term. [8] We found that women with obesity have a reduction in MAPSE between the second and third trimester, which could indicate early cardiac decompensation in this group. Right heart function, as assessed by TDI s' and TAPSE, were lower in obese compared to normal BMI women, in accordance with findings outside the setting of pregnancy, suggesting suboptimal right heart function in obesity.[42]

The relationship between obesity and hypertension outside and during pregnancy is well documented. [43, 44] Obesity increases the risk of hypertensive disorders compared to normal BMI pregnant women and it has been reported that this risk doubles with each 5 to 7 unit increase in pre-pregnancy BMI. [45] It is conceivable that maternal obesity induced insulin resistance can be associated with reduced cytotrophoblast migration and uterine spiral artery remodelling, which leads to placental hypoxia and ischemia, which in turn can result in the release of anti-angiogenic and inflammatory factors into the maternal circulation promoting endothelial dysfunction, reduction in nitric oxide production, increase in oxidative stress and finally the development of PE. [46] More recently, it is thought that the maternal cardiovascular system plays a pivotal role in the pathophysiology of PE; the risk factors for PE are cardiovascular in nature, cardiovascular signs and symptoms predominate the clinical picture of PE and cardiovascular morbidity persists for decades after PE. [13, 46] In accordance with this notion, higher early pregnancy maternal BP, maternal hyperdynamic circulation with high CO and low resistance have been described prior to the onset, as well as, during the clinical phase of late PE.[23, 47, 48]With regard to cardiac geometry, it has been reported that 50% and 20% of pregnant women destined to develop PE have evidence of cardiac remodelling, with higher RWT, and concentric hypertrophy, respectively. Additionally, diastolic function has also been shown to be reduced prior to the onset of PE. [49, 50] We have found that obese pregnant women have features of a hyperdynamic circulation with higher BP and CO, lower PVR, LV hypertrophy and reduced diastolic indices; characteristics that may render these women more susceptible to the development of hypertensive disorders during pregnancy and explain their high prevalence in obese pregnant women. [10]

Strengths and limitations

All echocardiographic examinations were performed and analysed by experienced operators and the longitudinal design adds strength to our findings. However, the examinations were technically challenging in the obese group and two patients were removed from analysis due to inadequate quality. Women who attended a minimum of two out of three scans were included, four women had two rather than three scans (two from

each group). Although the number of women with normal BMI was low, the findings in that group were consistent with the published literature.[8]

Conclusion

Pregnant women with obesity, have altered maternal hemodynamic function (higher BP, CO, lower PVR) and cardiovascular geometry (higher LV mass and LV hypertrophy) with suboptimal diastolic and longitudinal function compared to women with normal BMI. The impact of these changes on the long-term maternal and perinatal outcomes remains to be determined.

Disclosure statement

The authors report no conflict of interest.

Contribution to authorship

DP and MS conceptualised and planned and the study. The recruitment, echocardiograms and analysis were carried out by DP and MV. The interpretation and first draft was written by DP. The discussion was further developed with the assistance of MS and the paper was reviewed by GS.

Consent

Informed written consent to participate in the study and publication was obtained from all participants.

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Ethical approval

The study protocol was approved by the National Health Service Research Ethics Committee (reference number, 14/LO/0592), February 2018.

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