Maternal cardiovascular adaptation to pregnancy in women with previous bariatric surgery and obese pregnant women

Dr Deesha Patel MBBS BSc MRCOG
2018-2021

PhD Thesis

Supervisors: Miss Makrina Savvidou, Professor Mark Johnson &
Professor Giovanni Di Salvo

Institute of Reproductive and Developmental Biology
Department of Metabolism, Digestion and Reproduction,

Imperial College London

PhD Student
Dr Deesha Patel MBBS BSc MRCOG
Clinical Research Fellow
Institute of Reproductive and Developmental Biology
Department of Metabolism, Digestion and Reproduction
Imperial College London
Chelsea & Westminster Hospital
369 Fulham Road, London SW10 9NH
Email: deesha.patel@doctors.org.uk
Tel: +44(0)7877171363

Supervisors

Miss Makrina Savvidou MD FRCOG
Consultant in Obstetrics & Fetal Medicine
Institute of Reproductive and Developmental Biology
Department of Metabolism, Digestion and Reproduction
Imperial College London
Chelsea & Westminster Hospital
369 Fulham Road, London SW10 9NH
Email: m.savvidou@imperial.ac.uk

Professor Mark Johnson PhD FRCOG
Professor of Obstetrics
Institute of Reproductive and Developmental Biology
Department of Metabolism, Digestion and Reproduction
Imperial College London
Chelsea & Westminster Hospital
369 Fulham Road, London SW10 9NH
Email: mark.johnson@imperial.ac.uk

Professor Giovanni Di Salvo MD PhD MSc FESC FEACVI FISC
Consultant Cardiologist
Imperial College London
Royal Brompton Hospital
Sydney Street, London SW3 6NP
Email: giodisal@yahoo.it

This thesis is dedicated to my family

Overview

The prevalence of obesity in pregnancy is rising every year both in the UK and globally. Obese pregnant women are often of childbearing age and go on to have high risk pregnancies with increased risk of hypertensive disorders, gestational diabetes and large-for-gestational age neonates.

Bariatric Surgery is a highly successful treatment for sustained weight loss and its use in the management of obesity is growing. Studies of individuals before and after bariatric surgery, outside of pregnancy, have shown a reduction or resolution in hypertension, cardiac remodelling with reduced left ventricular mass and improved function. Numerous retrospective studies have shown that pregnancy following bariatric surgery is associated with a reduced risk of developing hypertensive disorders, however, the mechanisms for this are largely unknown. In pathological pregnancy complicated by pre-eclampsia or growth restriction, studies have shown cardiovascular alterations in haemodynamic indices, cardiac geometry and function, highlighting the importance of the cardiovascular adaptation to pregnancy.

This study is a prospective, observational study aiming to investigate the maternal cardiovascular adaptation to pregnancy in women with previous bariatric surgery compared to women with similar early pregnancy BMI and similar pre-surgery BMI. In addition, we investigated the cardiovascular adaptation to pregnancy in obese pregnant women compared to normal BMI pregnant women and the placental function in obese pregnant women and its association with cardiovascular parameters. Cardiovascular function was assessed at three time points during pregnancy by measuring blood pressure and using transthoracic echocardiography to assess haemodynamic function, cardiac geometry and systolic and diastolic function.

Statement of originality

All work presented in this thesis was performed by myself unless stated otherwise in the text.

Submitted in fulfilment of the requirements for the degree of Doctor of Philosophy at Imperial College London

Deesha Patel

Copyright declaration

Acknowledgements

Firstly, I would like to thank my supervisors Miss Mina Savvidou, Professor Mark Johnson and Professor Giovanni Di Salvo for all their guidance over the last 3 years. In particular, I would like to thank Miss Savvidou for the huge amount of time and effort that she dedicated to this project from initial concept all the way through to thesis writing and publication. I am incredibly grateful for the opportunity and the skills gained along the journey. I hope to work together again in the future.

I would like to thank Dr Francois dos Santos for sharing his research room and his invaluable support and guidance at the start and along with Nooshin for all the emotional support, endless kind words and keeping me sane throughout. We had so many laughs along the way and I have many great memories. I would like to express my gratitude to Dr Nunzia Borrelli and Dr Martina Avesani for their patience in teaching me how to perform echocardiographs and their high standards and guidance.

Thank you so much to my Mum and sister, Minal for always being there for me and being so patient when I was always too busy and likewise my best friends Mehul, Angeli and Sandy. Lastly, I would like to thank to my husband Daniel for being so understanding, supportive and patient throughout this seemingly never-ending process!

Lastly, thank you to all the women who took part in the study and made this possible.

Conference presentations

1. Maternal cardiovascular adaptation to pregnancy in women with previous bariatric surgery.
   RCOG World Congress, June 2021 – **Prize Best Oral Presentation in session**

2. Maternal cardiovascular adaptation to pregnancy in obese women
   RCOG World Congress, June 2021

3. Maternal cardiovascular adaptation to pregnancy in women after bariatric surgery
   RCOG Annual Academic meeting, February 2021

4. Maternal cardiovascular adaptation to pregnancy in in obese pregnant women compared to normal BMI pregnant women
   RCOG Annual Academic meeting, February 2021

5. Maternal cardiovascular adaptation to pregnancy in women after bariatric surgery.
   National Trainees Conference, May 2021

   Cardiovascular maladaptation in obese pregnant women, a longitudinal study
6. National Trainees Conference, May 2021

Publications

1. Bourke M, Patel D, Rocca A, Maric T, Savvidou M. Effect of post-bariatric maternal weight loss and surgery to conception interval on perinatal outcomes of nulliparous women. Surgery for Obesity and Related Diseases. Volume 17, Issue 8, 1473 - 1479

2. News article
   Bariatric Surgery Leads to Better Cardiovascular Function in Pregnancy
   Medscape, https://www.medscape.com/viewarticle/953588

3. Paper submitted and undergoing corrections for publication
   Maternal cardiovascular adaptation to pregnancy in women with previous bariatric surgery. American Journal of Obstetrics and Gynaecology

Contents

List of Tables

Chapter 5

Chapter 6

Chapter 7

Table 7.2. Univariate analyses of surgery, maternal demographic and pregnancy characteristics with fetal growth rate and birthweight

List of Figures

Chapter 4

Chapter 5

Chapter 6

Chapter 7

Figure 7.1 Correlation of maternal pre-surgery to early pregnancy weight loss and fetal growth rate and birthweight

Abbreviations

β-hcg- Beta human chorionic gonadotropin
BMI- body mass index
BP- blood pressure
BPD-DS- Biliopancreatic diversion with duodenal switch
BW- birth weight
CO- cardiac output
CI-cardiac index
CSA- cross-sectional area
DBP- diastolic blood pressure
EF-ejection fraction
EDV-end diastolic volume
ESV-end systolic volume
GDM- gestational diabetes
GLS-global longitudinal strain
GCS-global circumferential strain
HR - heart rate
IUGR - Intrauterine fetal growth restriction
IVS-intraventricular septum
LA- left atrium
LGA- large-for-gestational age
LVEDD-left ventricle end diastolic diameter
LV- left ventricle
LVM-left ventricular mass
LVOT-left ventricular outflow tract
MAP- mean arterial pressure
MAPSE- mitral annular plane systolic excursion
MBRRACE- Mothers and Babies: Reducing Risk through Audits and Confidential Enquiries across the UK
NICE- National Institute of Clinical Excellence
PAPP-A- pregnancy associated plasma protein A
PE- pre-eclampsia
PVR- peripheral vascular resistance
PW- posterior wall (left ventricle)
RV- right ventricle
RWT-relative wall thickness
RYGB- Roux-en-Y gastric bypass
SBP- systolic blood pressure
SGA- small-for-gestational age
STE- speckle tracking echocardiograph
SV- stroke volume
SVI-stroke volume index
SVR- systemic vascular resistance
TAPSE- tricuspid annular plane systolic excursion
TDI- tissue doppler imaging
TRP- total peripheral resistance
TVR- total vascular resistance
UtPI- uterine artery PI
VTI- velocity time integral

Chapter 1

Introduction

Obesity

Overweight and obesity are defined as excessive fat accumulation that presents a risk to health. (1) A crude population measure of obesity is the body mass index (BMI), a person's weight (in kilograms) divided by the square of his or her height (in metres). Obesity is defined as a BMI≥ 30 and a BMI≥ 25 is considered overweight (Table 1.1). (2).

Table 1.1. National Institute of Clinical Excellence (NICE) BMI classification

Classification	**BMI**
Healthy weight	18.5–24.9 kg/m^2
Overweight	25–29.9 kg/m^2
Obesity Class I	30–34.9 kg/m^2
Obesity Class II	35–39.9 kg/m^2
Obesity Class III	40 kg/m^2 or more

Obesity has nearly tripled since 1975 and the World Health Organisation estimate that in 2016 more than 1.9 billion adults (39%) worldwide were overweight and 650 million (13%) were obese (Figure 1.1). (1, 2) In the UK this epidemic is perpetuated and in 2018 60% of women in England were overweight or obese and 29% obese. Many of these woman are of childbearing age and go on to have high risk pregnancies. (3)

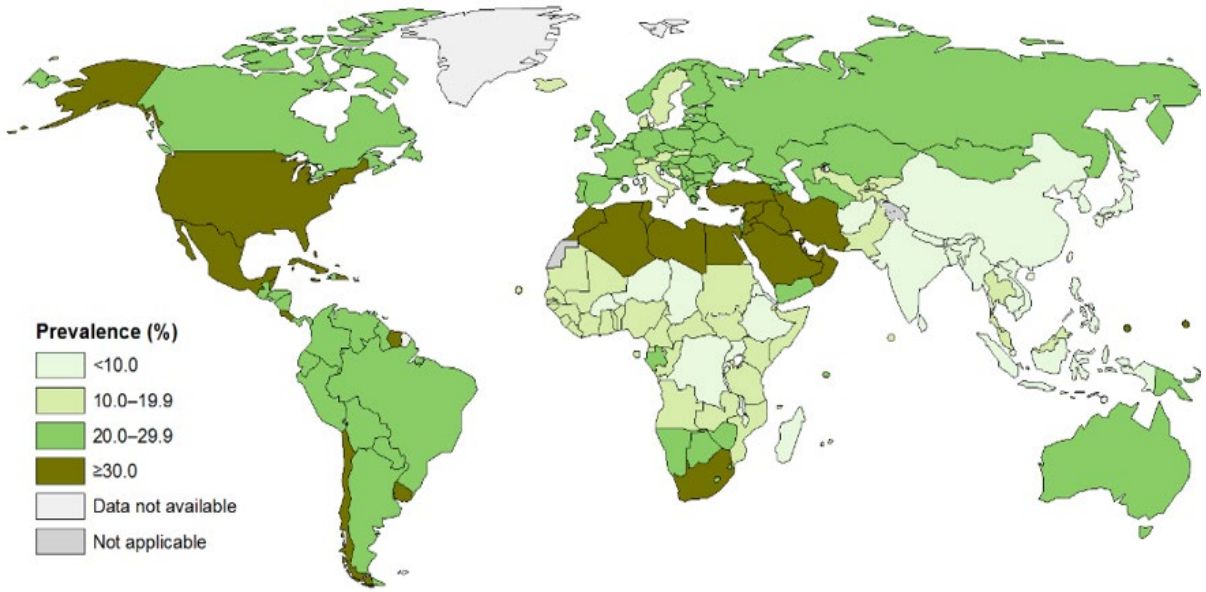


Figure 1.1 Prevalence of obesity in women ages 18 years and over (BMI>30). Adapted from the World Health Organisation. (2)

Obesity is associated with increased risk of cardiovascular disease, diabetes, cancer and death.(4) By 2030, it is estimated that there will be 11 million more obese adults in the UK and the combined medical cost of preventable diseases associated with obesity is £1·9–2 billion/year.(5)

Obesity and the cardiovascular system

Haemodynamic changes

Obesity results in a hyperdynamic circulation with increased blood volume to meet the perfusion demands of the increased adipose tissue (Figure 1.2). The cardiac output (CO) is raised due to an increased stroke volume (SV) and heart rate (HR). (6) Obesity causes hypertension by mechanisms involving abnormal renal pressure natriuresis and increased renal sodium reabsorption by activation of the renin-angiotensin aldosterone (RAAS) and sympathetic nervous system (SNS). Excess visceral adipose tissue can physically compress the kidneys, increasing intrarenal pressure and tubular reabsorption. (7) The mechanism of SNS activation is not fully understood but thought to involve leptin and the brain melanocortin system as well as hyperinsulinaemia. (8-10) Furthermore, there is an association between visceral fat and raised aortic stiffness which contributes to increased afterload and the development of hypertension. (6, 11) Obesity and insulin resistance interact and impair

vascular structure and function that are linked to endothelial dysfunction, increased artery intima media thickness and increased vascular stiffness. Recently, dysfunctional perivascular adipose tissue adjacent to the vessel wall is thought be involved in the mechanism of vascular stiffness. The pathophysiology involves complex mechanisms that are not completely understood.(12)

Cardiac Geometry

Obesity causes changes in cardiac morphology, most notably augmentation of the left ventricle (LV) leading to hypertrophy, demonstrated by an increased LV mass. (13) A meta-analysis has shown that obese individuals are four times more likely to develop LV hypertrophy. (14) Obesity is associated with increased stroke workload owing to an increased preload and stroke volume leading to left ventricular dilatation, which in turn causes a rise in wall stress and increasing myocardial mass to compensate. Left ventricular diastolic diameter is increased and correlates with LV mass, this LV dilation is needed to compensate for increased venous return and results in eccentric and concentric patterns of hypertrophy. Eccentric hypertrophy, more commonly found in obesity, occurs where there is normal global LV wall thickness with increased cavity size and LV mass. The duration of obesity has been shown to correlate directly with LV diastolic chamber size, wall thickness and mass. (6, 13, 15)

As well as LV changes, obesity is associated with left atrial (LA) enlargement which positively correlates with BMI. (13) This is initially due to a high intravascular volume and venous return but other factors such as ventricular hypertrophy and abnormal filling also contribute. (6, 13)

Limited data exists relating to right ventricle (RV) morphology in obesity. The largest study has shown that RV mass and end-diastolic volume are both greater in the obese compared to lean individuals. (16)

Cardiac function

Atrial and ventricular remodelling are known to predispose to impaired function. (6) Obesity related hypertrophy causes three main changes; myocyte hypertrophy, accumulation of fibrous tissue within cardiac interstitium and increased epicardial adipose mass, which can lead to alterations in tissue texture and compliance. (17, 18) These variations can lead to diastolic

dysfunction due to altered ventricular filling as a result of abnormal relaxation of the ventricle, increased mass and therefore greater reliance on atrial contraction. (6, 19)

Ejection fraction (EF) is the volume of blood expelled from the ventricle with each cardiac cycle. (20) The LV systolic function measured by EF is usually preserved or even raised in early obesity (13, 19). However, some studies using load independent methods to assess systolic function, including tissue Doppler imaging (a measurement of the velocity of the myocardium) and strain rate imaging (a measure of global deformation of the myocardium) (21), have found subclinical systolic dysfunction in obese individuals. (13, 22, 23) Factors contributing to this LV systolic dysfunction include duration of obesity, diastolic impairment, increased LV mass and co-morbidities such as coronary artery disease and hypertension. (13) When considering cardiac changes in obesity the most significant ones relate to left ventricular hypertrophy due to its high prevalence and its strong association with adverse cardiac outcomes. (24)

Studies of the RV in obesity are limited and with varying results. Diastolic and systolic function have been reported as reduced; (25, 26) however, a study using cardiac MR found no change in right ventricle EF. (27) It is also known that obesity is associated with obstructive sleep apnoea and pulmonary hypertension this can lead to RV hypertrophy and eventually dysfunction. (13) Figure 1.2 summarises some of the changes to the cardiovascular system in obese individuals.

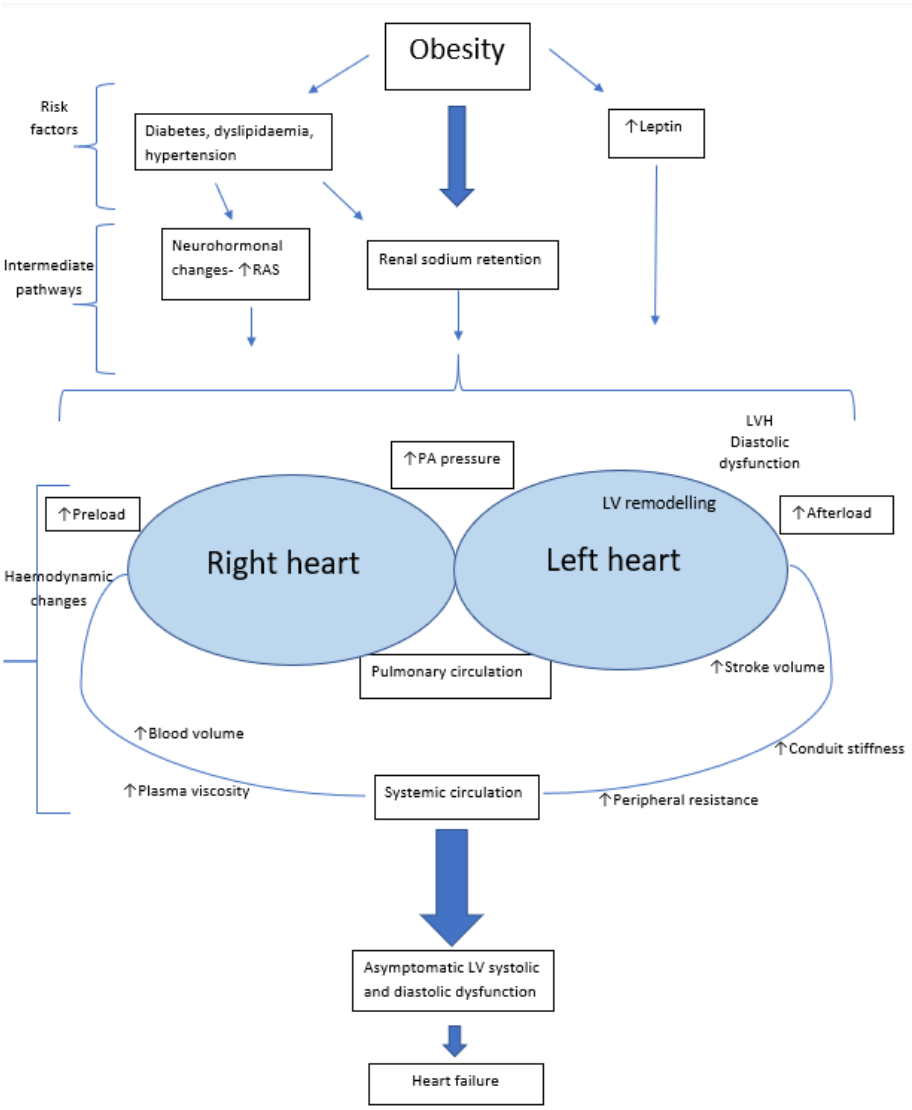


Figure 1.2. Obesity and cardiac dysfunction: mechanisms. Adapted from Vasan S.(6) *LVH*, left ventricular hypertrophy; *RAS*, renin–angiotensin system

Cardiovascular changes pregnancy

Normal pregnancy

Haemodynamic changes

Normal pregnancy is associated with significant maternal cardiovascular and haemodynamic changes (Table 1.2).

Table 1.2 Cardiovascular changes in pregnancy. Adapted from May L.(28)

Heart Rate	⇑
Systolic Blood Pressure	⇔
Diastolic Blood Pressure	⇔ / ⇓
Stroke Volume	⇑
Cardiac Output	⇑

These changes begin in early pregnancy as blood volume must increase in order to provide sufficient oxygenation to the enlarging uterus, fetus and placenta. From 6 weeks of gestation, hormonal changes initiate this process. The primary drive is peripheral vasodilation mediated by nitric oxide, oestradiol and prostaglandins. Systemic vasodilation and increased vascular capacitance cause an underfilled vascular system which leads to plasma volume expansion. (28-30) Oestradiol activates the RAAS which leads to increased sodium reabsorption and plasma volume expansion by almost 50%. Human placental lactogen stimulates erythropoietin production from the kidneys which increases the red cell volume but to a lesser extent, around 18%. This disproportionate increase in maternal plasma volume and red blood cells is responsible for the physiological dilutional anaemia and decreased viscosity in pregnancy. (30, 31) Oestradiol mediated endothelial nitric oxide production results in vasodilation and reduced systemic vascular resistance (SVR) and therefore, ventricular afterload. (32) Systemic vascular resistance decreases from 8 weeks of gestation to a nadir at 28 weeks and a slight increase at term. (28, 33) Changes in resistance can impact blood pressure (BP). Mean arterial blood pressure (MAP) is the average arterial pressure during a single cardiac cycle which is important for organ perfusion. MAP is directly proportional to CO and SVR. (32) During normal pregnancy, MAP typically decreases approximately 5 to 10 mmHg by the middle to end of the second trimester and increases back towards pre-pregnancy levels as term approaches. (28, 33) Despite the reduction in SVR, there is only a small decrease in maternal MAP, mainly due to increased CO (Figure 1.3). (28) Systolic blood pressure (SBP) tends not to change significantly during pregnancy and most studies conclude that diastolic blood pressure (DBP) decreases in the first and second trimesters but increases in the third trimester .(33)

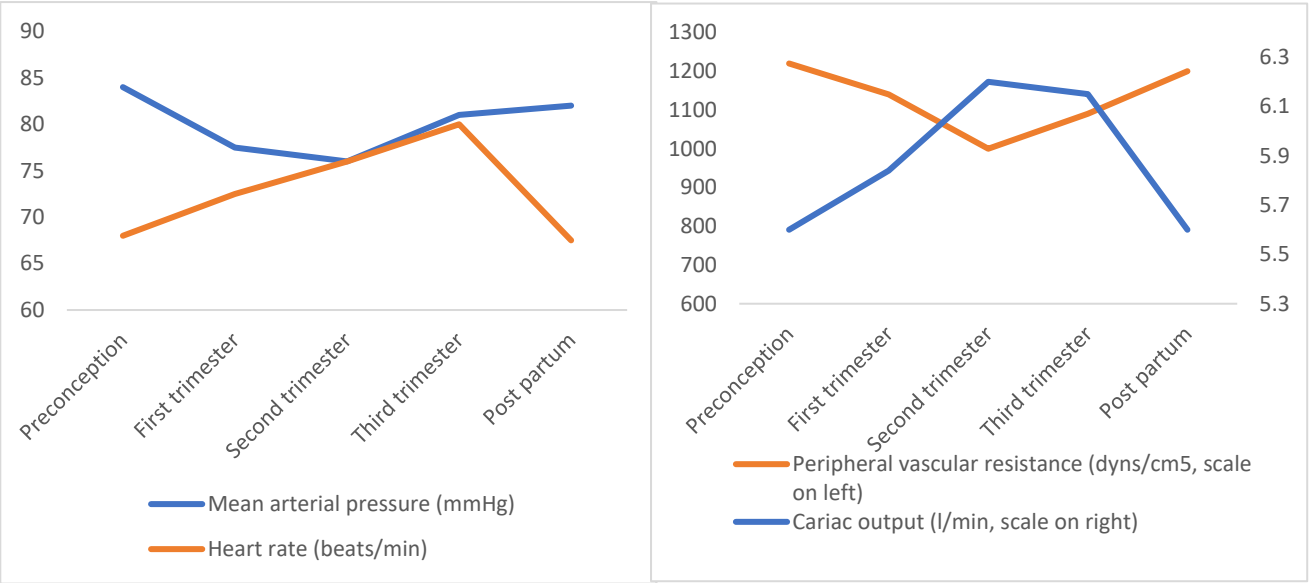


Figure 1.3. Cardiovascular changes from pre-conception to post-partum: changes in mean arterial pressure, heart rate, cardiac output and peripheral vascular resistance from pre-conception through pregnancy to post-partum. Adapted from Foo L.(34)

Cardiac output is the product of stroke volume (SV) and heart rate (HR), the stroke volume is the amount of blood entering the aorta during each cardiac cycle and is dependent on preload and afterload. The preload is increased in pregnancy and the afterload is reduced due to smooth muscle relaxation (vasodilation) resulting to reduced resistance. These factors are responsible for an increase in SV; by the end of the first trimester there is 20–30% increase which peaks over 30% at around 24 weeks, thereafter studies report varying results of maintenance, increase or decrease. (28, 33) Maternal HR increases from around 4 weeks of gestation and continues to rise until it plateaus in the third trimester where it is around 15-20 beats per minute (bpm) higher than pre-pregnancy. The increased HR occurs via increased sympathetic tone and decreased parasympathetic tone. (28, 32) The above changes in SV and, to a lesser extent, in HR lead to a 30-50% increase in maternal CO which starts as early as 6 weeks of gestation, peaks at 20-28 weeks and is then maintained until term.(32, 35, 36) A study of normal pregnancy have reported CO values ranging from 5.7 l/min in the first trimester to 6.8 l/min at term. The above findings are summarised in Table 1.3. (37)

Table 1.3. Maternal Cardiovascular Function in Normal Pregnancy. Adapted from Melchiorre K. Data are expressed as median (interquartile range)

Parameter	Non pregnant	1st Trimester	2nd Trimester	3rd Trimester	Term
HR, bpm	71 (66–75)	75 (69–82)	76 (71–85)	82 (75–89)	79 (72–87)
SBP, mm Hg	110 (100–115)	100 (90–106)	100 (98–110)	100 (98–110)	110 (100–120)
DBP, mm Hg	70 (60–80)	63 (60–70)	68 (60–72)	70 (60–72)	70 (60–75)
MAP, mm Hg	83 (71–90)	77 (70–83)	79 (73–83)	83 (73–87)	83 (74–90)
SV, ml	70 (66–79)	76 (66–87)	78 (67–93)	80 (69–97)	83 (76–95)
CO, l/min	4.9 (4.3–5.8)	5.7 (5.1–6.5)	5.9 (5.0–7.3)	6.4 (5.4–7.8)	6.8 (6.0–7.7)

Cardiac geometry

The anatomy of the heart changes during pregnancy. The heart is pushed upwards and rotated forward as the diaphragm is pushed up by the expanding uterus. There is physiological hypertrophy to cope with increased preload. Ventricular hypertrophy increases contractility and contributes to the rise in SV. End diastolic volume is increased via increased ventricular mass and valvular diameters and this is despite a reduced filling time and a shorter cardiac cycle due to higher HR. Although the heart is dilated due to the increased end diastolic volume and ventricular hypertrophy, EF is maintained. (28, 32) The left atrium (LA) diameter increases by around 15% throughout pregnancy up to 34 weeks due to an increased preload and CO. Left ventricular end-diastolic dimension increases by around 10% due to increased preload and LV end-systolic dimension increases by around 20% due to increased HR and afterload. LV wall thickness increases by 15-25% starting from 12 weeks and this allows for the increased preload and minimises wall stress. Left ventricle wall mass increases by 50%, mainly in the third trimester, even when corrected for body surface area (LV mass index) implying true hypertrophy. The LV outflow tract increases slightly due to the hemodynamic changes described. All the above changes are needed to maintain the increased cardiac workload required in pregnancy. (33)

Cardiac function

Systolic function

The radial function of the LV is due to contraction of the circumferential myocardial fibres (Figure 1.4) and is often evaluated by ejection phase indices such as: EF, fractional shortening and velocity of circumferential fibres shortening. Studies of these indices in pregnancy have given conflicting results with some showing better function and some showing no change; this may be due to different methodology used. Traditionally, LV systolic function is measured by radial fibres of ejection phase indices, however longitudinal fibres are more susceptible to ischemic and hypertensive changes. (33) Left ventricular longitudinal function, assessed by long axis displacement and compared to non-pregnant controls, has been shown to increase with gestational age to a maximum of 12% at mid pregnancy and then subsequently decline towards term. (38, 39) Systolic function, assessed by myocardial velocity, has shown differing results of no change with gestation (39) or a decrease by term. (37, 40)

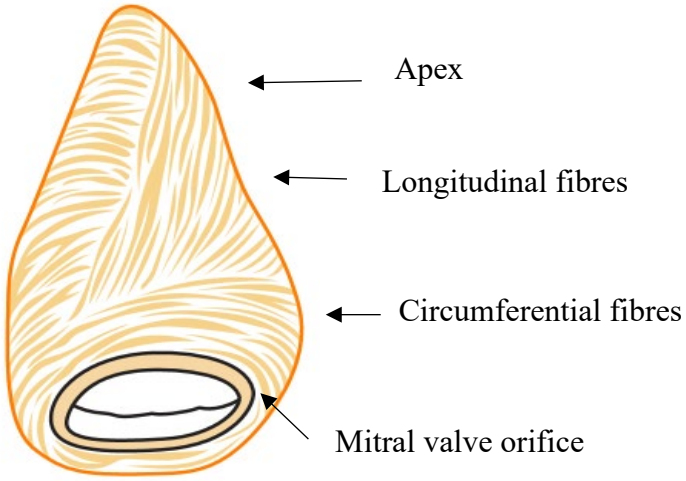


Figure 1.4. Schematic representation of the arrangement of fibres of the left ventricle. Adapted from Kaddoura S. (41)

Deformation imaging is a relatively new technique to evaluate systolic function and measures the differences of motion and velocity between regions of the myocardium throughout the cardiac cycle. Deformation is measured by strain indices which can be assessed using tissue Doppler imaging (TDI) or speckle tracking echocardiography (STE). (21) Studies of STE in pregnancy are limited but have shown that global strain can detect a significant decrease in function between the second and third trimester where EF showed no significant change. (42, 43)

Diastolic function

Diastolic function is commonly assessed by mitral valve inflow using pulsed wave Doppler. E represents the peak velocity of blood flow from gravity in early diastole and A is the peak velocity flow in late diastole caused by atrial contraction. An abnormal E/A ratio suggests impaired left ventricular filling and diastolic dysfunction. In normal pregnancy, studies have shown that the E/A ratio falls with advancing gestation indicating a greater reliance on atrial contraction. (33) The deceleration time is the time from the maximum velocity of the E wave to return to zero and in normal pregnancy this is reported to decrease from the first to the second trimester and then remain relatively stable. (37) The LV filling pressure (assessed by E/E') has been shown to increase at term when compared to the second trimester. (37) Overall, these diastolic indices are influenced by physiological adaptations in HR, preload, LV compliance and contractility. (44)

Pathological pregnancy

In recent years maternal cardiovascular function has been associated with adverse maternal and neonatal outcomes. Maternal cardiovascular mal-adaptation has been implicated in the pathophysiology of placenta-related pregnancy complications such as pre-eclampsia (PE) and/or intra-uterine fetal growth restriction (IUGR). (45, 46) Pre-eclampsia is the leading cause of maternal morbidity and mortality in the developed world with a prevalence of around 2-5%. (47-49) It is thought to derive from abnormal development of the placenta leading to inadequate perfusion and endothelial dysfunction. In recent years studies have linked cardiovascular risk factors with the development of PE and it is now thought that the cardiovascular system plays a vital role in the development of the disease. It is suggested that placental hypoxia is related to the cardiovascular functional reserve and the ability to adapt to pregnancy. (47) Shared risk factors of cardiovascular disease and PE include obesity, age, ethnicity, smoking, chronic kidney disease, stress, polycystic ovarian syndrome and diabetes. Further to this, for women who develop PE, the risk of cardiovascular morbidity post-partum as well as later life is increased. (47, 50, 51)

Normal pregnancy has been described as a stress test for the heart due to the excess volume load and it has been reported that in normal pregnancy, a small but significant proportion of women have an excessive increase in the LV mass and remodelling with associated diastolic dysfunction at term. (37, 52) A study of women before conception and into pregnancy demonstrated that women who went on to develop PE had a decreased CO and raised total

peripheral resistance (TPR) pre-pregnancy compared to those who had uncomplicated pregnancies. (46) An echocardiographic study of women in the second trimester, prior to the diagnosis of PE, found evidence of LV concentric remodeling and in those with preterm PE (delivery before 37 weeks) there was a low CO and high resistance with diastolic and systolic dysfunction. (53) A large systematic review of cardiovascular function in women with gestational hypertension (GH) or PE included 36 studies (N=745 women with GH and N=815 women with PE), they reported that in pregnancies complicated by hypertensive disease, LV mass was increased with concentric remodeling. Diastolic function was impaired with a reduction in E/A ratio and an increase in the ratio of early diastolic mitral inflow velocity and early diastolic mitral annular velocity (E/E′) indicating increased filling pressure. There was no difference in systolic function in most studies. Cardiac output varied in studies, early trimester studies before the onset of PE showed a hyperdynamic circulation with high cardiac output and low resistance, whereas, in the second trimester women who went on to develop PE had lower CO and higher resistance. In the clinical phase of PE there was a hemodynamic crossover with reduced CO and high resistance. (54)

Pre-eclampsia can be divided into early (<34 weeks) and late onset (>34 weeks) and it is thought that they develop through different models of cardiovascular adaptation to pregnancy resulting in different hemodynamic states. A study of early and late PE found that early onset PE was associated with a low CO and high resistance whereas late PE demonstrates the opposite profile; high CO and low resistance. Early PE is related to impaired placental vascular remodeling often with fetal growth restriction and hemodynamically results in a low volume and high resistance state. Late PE is thought to be related to maternal factors such as BMI and age and hemodynamically results in a high volume and low resistance state. (55) A recent longitudinal study of women from 24 weeks gestation to term found that women who developed PE had a high CO and low resistance at early and late gestations. However, if PE was associated with growth restriction, there was low CO and high resistance. (56) This differs from other studies that suggest low CO and high resistance in early PE (45) and may be explained by PE and growth restriction often coexisting at early gestational ages and uncommonly in late PE.

Another theory suggests that both early and late PE result from placental dysfunction however with different causes and timing of placental under perfusion. In early PE there is incomplete spiral artery invasion whereas in late PE there is an aging placenta which is restricting

intervillous perfusion. Early and late PE result in syncytiotrophoblast stress and release of pro-inflammatory factors and maternal factors may increase the risk for both early and late PE. (57)

Studies have also found associations between CO, TPR and birth weight (BW). A study conducted at 35-37 weeks of gestation reported significant positive associations between maternal CO/HR and birth weight (BW) but significant negative associations between TPR/BP and BW. (58) A study of pre-pregnancy maternal CO found that the increase in CO and the reduction in peripheral vascular resistance (PVR) both correlated with BW with the most substantial adaptations in CO and PVR occurring early in the first trimester. The timing of these changes occur prior to the development of a functional placental unit at 12 weeks, suggesting that important adaptations of maternal cardiovascular hemodynamic indices precede placental development. (59)

Obesity in Pregnancy

Obesity in pregnancy is associated with an increased risk of miscarriage, gestational diabetes (GDM), hypertensive disorders, PE, venous thromboembolism, induction of labour, dysfunctional/prolonged labour, caesarean section, anaesthetic complications, post-partum haemorrhage, wound infections and mortality. (60) In particular, studies have reported that the prevalence of pregnancy-induced hypertension is 9.1%-10.2% in obese women and 12.3% in the morbidly obese women. (61) A systematic review of 52 studies reported that the risk of PE is increased by 50% in women with a high booking BMI (62) and that the risk of PE doubles with each 5 to 7 kg/m^2 increase in pre-pregnancy BMI. (63) A study investigating incremental increases in obesity found that overall obese mothers were almost three times more likely to develop PE (usually late-onset) compared to women with a normal BMI; their results displayed a dose dependent relationship with morbidly obese women having the highest incidence, around five-fold higher than women with normal BMI. (64)

The mechanisms underlying the association between hypertensive disorders and obesity are complex and likely to be related to insulin resistance, metabolic syndrome and inflammation leading to oxidative stress and vascular dysfunction. (65, 66)

The 2108 MBRRACE-UK (Mothers and Babies: Reducing Risk through Audits and Confidential Enquiries across the UK) report found that of the women who died from all causes, over one third (37%) were obese and of those that died from thrombosis/thromboembolism, 57% had a BMI above 30 and a further 16% had a BMI above 25. (67)

Babies of obese mothers are also at increased risk of complications such as congenital anomalies, stillbirth, prematurity, macrosomia and neonatal death. (68) In childhood, they are at increased risk of developing obesity and metabolic syndrome (60) which is thought to be related to "fetal programming". (69)

Obesity and the maternal cardiovascular system

There are a limited number of studies investigating the effect of obesity on the maternal cardiovascular system with conflicting results. A small study in the third trimester of pregnancy (N=15) found that, compared to normal weight women, obese pregnant women had an elevated MAP and increased LV mass with significant hypertrophy but no difference in CO or diastolic indices. (70) Similarly, another small study of morbidly obese pregnant women (N=8) reported greater LA size, LV wall thickness, interventricular septal thickness and LV mass with significant hypertrophy but similar systolic function compared to the non-obese mothers.(71) Conversely, a study of 40 obese individuals compared to women with BMI <30 reported that obese women had higher BP, CO, CO index, LV mass and relative wall thickness with higher incidence of diastolic dysfunction (40% vs 12.5% respectively) . Furthermore, to assess systolic function they used LV global longitudinal strain and found reduced function in the obese group. (72) In contrast, a study of 23 morbidly obese pregnant women that corrected for body surface area (BSA) found that SV index and CO index were significantly lower and SVR index was significantly higher in the obese group, they conclude that this may be associated with the increased prevalence of PE in this population. (73) A longitudinal study of circulation (N=232) reported a high volume/low-resistance circulation in the first and second trimester, however, in the third trimester, CO of obese women decreased which was not the case for nonobese women. Simultaneously, the persistently lower PVR in the obese group disappeared in the third trimester (74). All the above differences suggest that obesity is associated with a maladaptive cardiovascular response to pregnancy.

Bariatric surgery

Surgery and weight loss

Obesity is associated with increased risk of cardiovascular disease, diabetes, cancer and mortality. (4) Weight loss achieved by diet modification and exercise may improve cardiovascular risk profile (75) but, in the majority of patients, lifestyle changes and pharmacological interventions do not achieve long term weight loss. (76, 77) Bariatric surgery is a successful treatment for sustainable weight loss and achieves around 55% excess body weight loss across different surgical methods. (78, 79) Studies on long-term follow-up of patients after bariatric surgery showed significant reductions in mortality from heart disease, diabetes and cancer with a 40% reduction in mortality by any cause. (80) The National Institute for Health and Care Excellence (NICE) guidelines on obesity recommend bariatric surgery for a BMI≥ 40 or 35-40 with comorbidities such as diabetes or hypertension. (81)

There are two main types of bariatric surgery: the restrictive (gastric band/ sleeve gastrectomy) and malabsorptive/combined (gastric bypass) (Figure 1.5).

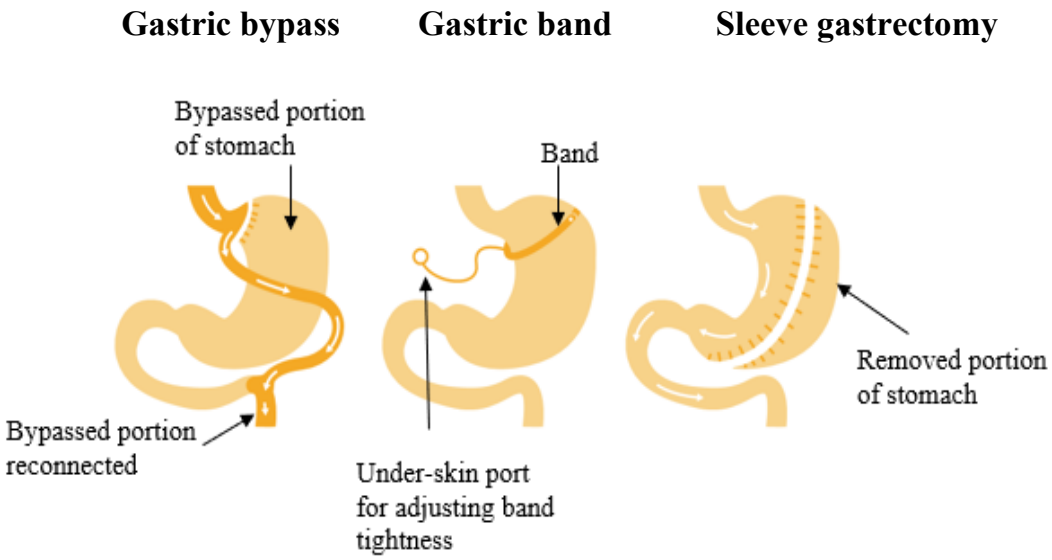


Figure 1.5. Type of bariatric surgery. Adapted from National Institute of Health Research (NIHR) Southampton Biomedical Research Centre (82)

Restrictive surgery

These procedures limit the amount of food in the stomach and include gastric band surgery and sleeve gastrectomy.

- Adjustable gastric band is a minimally invasive laparoscopic procedure where a ring with an inner inflatable band is placed around the fundus of the stomach to create a small pouch. The amount of fluid in the band can be adjusted via a port placed under the skin. It has a low rate of complications however compared to other methods the weight loss is lower, around 40-50% of excess body weight. (83-85)
- Sleeve gastrectomy is a procedure in which the stomach is reduced to about 15% of its original size by removing a large proportion following the major curve. This leaves the stomach shaped like a sleeve or tube. It is an irreversible procedure that can be performed laparoscopically. It is more effective than the gastric band and can achieve around 60% reduction of excess body weight; comparable to gastric bypass. The procedure is associated with alterations in gut hormones that suppress hunger, reduce appetite, improve satiety but there is potential for long-term vitamin deficiencies. (83-85)

Malabsorptive/ combined surgery

These procedures create a state of malabsorption in addition to the reduction in stomach size.

- Biliopancreatic diversion with duodenal switch (BPD-DS) is a procedure of two parts. The restrictive part is similar to the gastric sleeve. The malabsorptive part reroutes a large portion of the small intestine creating two pathways, the digestive loop takes food from the stomach to the common channel. Another pathway, the biliopancreatic loop carries bile from the liver to the common channel where it mixes with food and then empties into the large intestine. This surgery achieves the highest amount of excess weight loss, around 70%, with favorable changes in gut hormones to reduce appetite and improve satiety. However, there is a significant risk of deficiencies in protein and vitamins/minerals including iron, calcium, zinc and fat-soluble vitamins. (83-85)
- Roux-en-Y gastric bypass (RYGB) combines restrictive and malabsorptive methods and is the most commonly performed bariatric surgery. The first part is the creation of a small (15–30 ml) pouch from the upper stomach with bypass of the remaining stomach which restricts the volume of food. The second part involves dividing the proximal small intestine with the lower portion anastomosed to the gastric pouch and the upper allows transfer of gastric acid and enzymes from the bypassed stomach. RYGB achieves around 60% excess weight loss but can lead to vitamin/mineral deficiencies particularly in vitamin B12, iron, calcium, and folate.(83-85)

Bariatric surgery and the cardiovascular system

There are a number of studies investigating the effect of bariatric study on cardiovascular system. Appendix 1 summarises findings of some of these studies. Bariatric surgery is known to improve hypertension with some studies reporting improvement or resolution in 80% of patients. (10, 86-88) The mechanism for obesity-related hypertension is complex but, there appears to be an upregulation of the RAAS despite volume expansion. Increased angiotensin/aldosterone production may be mediated through several paths; adipocytes themselves can produce angiotensinogen and renal parenchymal compression due to visceral fat around the kidney can lead to decreased renal blood flow which is sensed by the macula densa and can lead to activation of RAAS. Furthermore, there is extra-adrenal aldosterone production via visceral adipocytes that is not influenced by traditional RAAS feedback dynamics. Along with RAAS upregulation, there is SNS activation that also plays a role and leads to increased baseline sympathetic tone. In recent years the role of hormones, cytokines and adipokines (such as leptin) have been thought to play an important role in the development of hypertension-related obesity. (10) This is supported by findings of a reduction in hypertension after surgery as soon as 10 day post-operative, prior to any significant weight loss (89, 90).

The entero-cardiac axis

Traditionally, it was thought that cardiac remodelling after bariatric surgery was solely due to haemodynamic changes, such as lowering of the BP, and weight loss. (91) However, it is now accepted that the metabolic components of bariatric surgery that contribute to cardiac reverse remodelling include the systemic BRAVE effects (**B**ile flow alteration, **R**eduction in gastric size, **A**natomical gut rearrangement, **V**agal manipulation and **E**nteric gut hormone manipulation). (91) Manipulation of the enteric gut hormones has been shown to have beneficial effects on the cardiac function via the entero-cardiac axis. (18, 91, 92)

Hormones such as secretin, glucagon and vasoactive intestinal peptide act as inotropes by activating cardiac membrane adenylate cyclase, a key enzyme in cardiac cell communication. Moreover, other key hormones, which are altered as a result of bariatric surgery, glucagon-like peptide-1 (GLP-1), leptin, adiponectin and ghrelin are also known to modulate cardiac function. (18, 91-93) Studies have found the plasma concentration of GLP-1 is increased after bariatric surgery (94, 95) and is involved in the stimulation of insulin secretion and insulin resistance, partly explaining the improved glucose tolerance after surgery. (96) In additionn,

GPL-1 has been found to have a natriuretic and diuretic effect (97, 98) which may contribute to the lowering of BP after surgery. (89) Leptin reduces appetite and increases the sympathetic nervous system. Obese individuals become resistant to satiety but preserve sympathetic activation in the kidney, heart and adrenal glands. Leptin has been shown to influence nitric oxide production and natriuresis in addition to chronic sympathetic activation to the kidney, it may cause sodium retention, vasoconstriction and an increase in blood pressure. (99) Studies have reported a reduction in leptin levels after bariatric surgery and a correlation between leptin and BMI. (100) Conversely, it has also been reported that after gastric bypass, leptin levels were lower than the similar BMI control group and comparable to normal weight individuals. (101)

Cardiac geometry

There is large body of evidence that bariatric surgery results in changes in cardiac structure. The most recent and largest meta-analysis by Aggarwal et al. (91) used pooled data of 40 studies in 1486 patients that were reviewed before and after surgery with follow up ranging from 3 to 45 months. Thirty-seven studies used echo data and 5 used cardiac MR. Overall, the study found that bariatric surgery resulted in favourable changes in cardiac geometry including reduction in LV mass, LV end diastolic and end systolic volumes.

Data on right heart structure is limited, a large study reported non-significant reductions in RV length, diastolic and systolic area following surgery. (102) Measures of RV size have been correlated with BMI. (102, 103)

Cardiac function

Left ventricular systolic function

The data is varied with some studies showing improvement and some no difference. (18, 91, 104, 105) The meta-analysis by Aggarwal et al.(91) reported systolic function (assessed as EF) pre and post-bariatric surgery and found that there was a small weighted mean increase of 1.198%. A study of 423 patients undergoing gastric bypass found no difference in EF before and after surgery or compared to an obese control group, however, at two year follow up, myocardial function as assessed by mid-wall fractional shortening increased and CO decreased in the surgery group compared to their pre-operative status.

Left ventricular diastolic function

In most studies, diastolic function was assessed pre- and post-surgery by the E/A ratio and LA dimensions. Several studies found an increase in E/A ratio and decrease in LA size or volume after surgery. (18, 91, 106).

Right heart function

Studies on RV systolic function are limited. Owan et al.(102) reported RV function, assessed by fractional area change in systole and diastole, as significantly higher post-surgery compared to the same individual before surgery as well as higher compared to a no-surgery obese group at 2 year follow up. Another smaller study of 57 patients using similar methods of assessment found no difference in RV function. (103). A study of 18 patient pre and post-surgery, using tricuspid annular plane excursion (TAPSE) and TDI, found no change in right heart function. (107)

Strain imaging

Studies assessing cardiac function measured by strain rate imaging which is thought to be superior to standard echocardiography, have found improvements in LV function pre and post-bariatric surgery. (108-110) Kaier et al.(108) used STE to measure global strain and found LV and RV global strain improved 6 months post-bariatric surgery.

Pregnancy after Bariatric surgery

Bariatric surgery has several maternal and neonatal implications, studies have shown that in women with previous bariatric surgery, there is a lower incidence of GDM, PE, and large-for gestational-age neonates, however, a higher incidence of small neonates and preterm birth. (111)

Bariatric surgery is associated with improvement in insulin sensitivity as marked by improvement in HOMA-IR index (homeostatic model assessment for insulin resistance index) which contributes largely to an improved glucose homeostasis.(112) Studies have shown pregnant women with previous bariatric surgery have reduced rate of GDM compared to obese women with no surgery (113, 114) but higher rate than normal weight pregnant women. (115) A large meta-analysis reported on studies that compared pregnant women after bariatric surgery with several subgroups including women matched for pre-surgery BMI, women matched for pre-pregnancy BMI and pregnancies in the same woman before and after surgery. The overall and subgroup analysis of women matched for pre-surgery BMI found lower incidence of GDM in the post-bariatric surgery group however when compared to pregnant

women matched for pre-pregnancy BMI there was no difference. (111) The same meta-analysis concluded an overall reduction in PE, by around 50%, in pregnant women after surgery with most studies using a control group of obese women; on reviewing their subgroup analysis there was non-significant (P=0.08) reduction in the post-bariatric surgery group compared to pregnant women matched for pre-pregnancy BMI. (111) Another review reported that the incidence of PE is lower in pregnancies of obese women after bariatric surgery compared to obese women without surgery concluding that the surgery improved outcomes even when obesity was still present, however, there were higher rates of PE than in normal weight women. (116) Further to this, studies of pregnant women after bariatric surgery matched to a similar pre-pregnancy BMI control groups have found lower rates of hypertensive disease indicating the effect of the surgery rather than weight was influencing the development of hypertensive disease. (117, 118) In addition, a large review paper concluded that bariatric surgery was associated with lower rates of maternal complications (hypertensive disorders and GDM) and these complications my approach community rates.(113, 119) A summary of some of the studies after bariatric surgery reporting on hypertensive disease in pregnancy have been given in Appendix 2.

Effects of bariatric surgery on the fetus include lower risk of large-for-gestational-age infants and of macrosomia however a higher risk for small-for-gestational-age infants and preterm birth. (111) With regard to mode of delivery studies found varying results but concluded no significant difference in caesarean section rates in women after bariatric surgery, compared to no surgery women. (111, 114)

The mechanisms underlying the above changes in pregnancy outcome are largely unknown. Maternal cardiovascular adaptation plays a pivotal role in maintaining a healthy pregnancy and mal-adaptation has been associated with fetal growth restriction and hypertensive disorders. Nevertheless, maternal cardiovascular changes in pregnancies following bariatric surgery have not been studied before.

Hypotheses

1. In pregnancies following bariatric surgery, maternal cardiovascular adaptation is altered compared to that of women with similar **pre-surgery** BMI.

2. In pregnancies following bariatric surgery, maternal cardiovascular adaptation is altered compared to that of women with similar **early pregnancy** BMI.
3. Pregnant obese women have a suboptimal cardiovascular adaptation to pregnancy compared to women with normal BMI
4. Maternal cardiovascular function is associated with placental function in overweight/obese pregnant women
5. Maternal weight loss, as a result of bariatric surgery, and surgery to conception interval can influence fetal growth and birth weight

Aims

The aims of the study are to:

Hypothesis 1: In pregnancies following bariatric surgery, maternal cardiovascular adaptation is altered compared to that of women with similar **pre-surgery** BMI.

1. Investigate longitudinally, the maternal cardiovascular adaptation to pregnancy in women following bariatric surgery compared to pregnant women with early pregnancy BMI similar to the pre-surgery BMI of the post-bariatric surgery women. Maternal cardiovascular system will be assessed using 2D echocardiography, including cardiac geometry, haemodynamic variables, systolic, diastolic and longitudinal function.
2. Investigate the association of maternal haemodynamic indices with birth weight in the above population

Hypothesis 2: In pregnancies following bariatric surgery, maternal cardiovascular adaptation is altered compared to that of women with similar **early pregnancy** BMI.

3. Investigate longitudinally, the maternal cardiovascular adaptation to pregnancy in women following bariatric surgery compared to women with similar early pregnancy BMI. Maternal cardiovascular system will be assessed using 2D echocardiography, including cardiac geometry, haemodynamic variables, systolic, diastolic and longitudinal function.
4. Investigate the association of maternal haemodynamic indices with birth weight in the above population

Hypothesis 3: Pregnant obese women have a suboptimal cardiovascular adaptation to pregnancy compared to women with normal BMI

5. To compare longitudinally, the maternal cardiovascular adaptation to pregnancy in women with BMI >30 with those with normal BMI. Maternal cardiovascular system will be assessed using 2D echocardiography, including cardiac geometry, haemodynamic variables, systolic, diastolic and longitudinal function.
6. To investigate the association of maternal haemodynamic function with birth weight in the above population.

Hypothesis 4: Maternal cardiovascular function is associated with placental function in overweight/obese pregnant women

7. Investigate the placental function in overweight/ obese pregnant women by assessing PAPP-A, β-hCG and uterine artery doppler
8. Investigate the association of maternal cardiovascular function and placental function, as assessed by PAPP-A, β-hCG, uterine artery doppler assessment and birth weight in overweight/obese pregnant women
9. Investigate the association of maternal cardiovascular function with birth weight in obese pregnant women

Hypothesis 5. Maternal weight loss, as a result of bariatric surgery, and surgery to conception interval can influence fetal growth and birth weight

10. Investigate the association between weight loss and fetal growth and birth weight
11. Investigate the association of surgery to conception interval and fetal growth and birth weight

Chapter 2

Materials and methods

The current thesis is part of a large prospective, observational study aiming to investigate the effects of obesity and in particular bariatric surgery on maternal and perinatal outcomes.

Regulatory approval

- Amendment to existing study Pregnancy in Overweight Women was achieved in February 2018 (REC 14/LO/0592)
- Health Research Authority approval was obtained in March 2018

Inclusion and exclusion criteria

Inclusion criteria

- Able to provide informed consent
- Singleton pregnancy
- Women of reproductive age: 18 to 50 years-old from one of the two groups below:
    - Pregnant women with previous bariatric surgery
    - Pregnant women without bariatric surgery

Exclusion criteria

- Unable to read and speak English to a fluency level adequate for the full comprehension of procedures required in participation and consent
- Any condition that, in the investigator's opinion, compromises the participant's ability to meet protocol requirements.
- Past medical history of significant cardiovascular condition or pre-existing hypertension

Patient recruitment

Electronic records of all bookings (CIMIS) were searched for via BMI to identify potential participants. Following the first trimester dating scan, participants were approached by members of the researcher team and recruited in the following groups:

- Group 1 – Pregnant women with previous bariatric surgery
- Group 2- Pregnant women without bariatric surgery matched for early pregnancy BMI, race and diabetes status.
- Group 3- Pregnant women without bariatric surgery matched for pre-surgery BMI, race and diabetes status
- Group 4- Obese pregnant women
- Group 5- Pregnant women with normal BMI

Advertisement posters were displayed in the antenatal clinic and ultrasound department areas at Chelsea and Westminster Hospital NHS Foundation Trust. The contact details (email and phone number) of the research team were provided.

Potential participants were approached by a member of the research team and invited to participate. The written patient information sheet was given or emailed to the patient. The contact details of a member of the research team were provided. Patients were given time to read and decide whether why wanted to participate in the study or not.

Visits

Participants were seen at time points during their pregnancy

- 11+0 -14+0 weeks
- 20+0 -24+0 weeks
- 30+0 - 32+0 weeks

Investigations

Maternal history and characteristics, including age, parity, racial group, method of conception and smoking status were recorded at the initial visit. Maternal weight prior to weight loss surgery and type and time of bariatric surgery, if any, were also recorded.

At each visit, maternal weight was taken to the nearest 0.1 kg using a calibrated electronic scale (Charder Electronic Co., Ltd. model MPPS-250), with the patient wearing light clothing and no footwear. Height was measured to the nearest 0.5 cm also without footwear. Maternal body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters (kg/m^2). (1) Medication history was also recorded as each visit.

Blood pressure measurements were performed manually using a sphygmomanometer (Accoson Dekamet, AC Cossor & Son (Surgical) Ltd, London, UK) according to the recommendations of the British Hypertension Society. (120) Two readings, 5 minutes apart, were taken from the left arm, in a seated position. The mean value was recorded.

Gestational age was calculated by the crown-rump length in the 1st trimester and combined screening test (nuchal translucency, pregnancy associated plasma protein and beta human chorionic gonadotropin) for the major chromosomal abnormalities was offered. (121, 122)

At each visit, fetal ultrasound scans were performed by an experienced operator (Miss Makrina Savvidou), using a 6MHz probe for abdominal and 5-9 MHz probe for transvaginal scans (Voluson E8 GE Healthcare system, USA). Fetal growth was estimated by the measurements of head circumference, abdominal circumference and femur length. The mean of two values was recorded and the Hadlock formula was used to calculate the estimated fetal weight at each time point. (123) Pulsed wave Doppler was used to assess the feto-placental circulation. Three consecutive waveforms for the umbilical and uterine arteries (assessed trans-vaginally) were obtained and the mean of two readings of the pulsatility index (PI) was recorded.(124-126)

At each visit, maternal cardiac function was assessed by two-dimensional and Doppler trans-thoracic echocardiography using the iE33 Ultrasound System (Philips Ultrasound, USA) equipped with a S5-1 transducer (frequency 1-5MHz) performed by an experienced operator (Dr Nunzia Borrelli and subsequently, the student submitting the current Thesis). In a number of patients maternal cardiac function was assessed using speckle tracking which is described later in this chapter.

All women underwent screening for gestational diabetes mellitus (GDM) at 28-30 weeks of gestation. Women with previous bariatric surgery underwent home glucose monitoring for 2 weeks and those with no previous bariatric surgery underwent a 2h-75g oral glucose tolerance test (OGTT). (127) GDM was defined according to NICE guidelines of fasting plasma glucose level ≥5.6 mmol/L and/or a 2-hour plasma glucose level ≥7.8 mmol/L.(128) Any pregnancy complications were recorded prospectively.

Hypertensive disorders of pregnancy included cases of pregnancy-induced hypertension and pre-eclampsia. Pregnancy-induced hypertension was defined as blood pressure greater than140/90 mmHg. (129) Pre-eclampsia was defined as hypertension after 20 weeks of gestation with proteinuria or other maternal organ dysfunction (including liver, kidney, neurological), or haematological involvement, and/or uteroplacental dysfunction. (130)

At delivery, birth weight was measured in grams. The gestational age at birth and weight were used to calculate the birth weight percentile. (131) Mode of delivery and delivery complications were also recorded.

Echocardiography

Echocardiography is the primary non-invasive imaging modality for assessment of cardiac anatomy, physiology, and function. Ultrasound is used to examine the heart and produce images and flow data generated by complex analysis of ultrasound waves reflected and backscattered from the patients' body. Sound waves are mechanical vibrations that cause alternate refraction and compression of any physical medium that they pass through. Sound is characterised by frequency and intensity; the frequency is measured in hertz (kilohertz, kHz and megahertz, MHz) which is oscillations per second. A frequency higher than 20kHz cannot be detected by the human ear and is called ultrasound, echocardiography uses ultrasound frequencies between 1.5 and 7.5 MHz. The speed that a sound wave travels through the body is the velocity of propagation, this is different for different types of tissue. Through the heart the velocity is 1540m/s whereas the speed in air is 330m/s. Wavelength is the distance from peak to peak of an ultrasound wave and it is calculated by dividing the frequency by the propagation velocity. In the heart, a frequency of 5MHz has a wavelength of 0.3mm. There is a trade-off between image resolution (shorter wavelength or higher frequency preferable) and depth penetration (longer wavelength or lower frequency preferable). Amplitude is the height of the ultrasound wave and a wide range of amplitudes can be displayed using a greyscale display for both imaging and spectral Doppler. Propagation of ultrasound waves in the body to generate ultrasound images and Doppler data depends on acoustic impedance and the primary determinant of this is tissue density. Soft tissues have a smaller difference in tissue density and acoustic impedance. Ultrasound is reflected from boundaries between tissues with differences in acoustic impedance (for instance blood and myocardium). The interaction of the ultrasound waves with the tissue can be described in terms of reflection, scattering, refraction and attenuation. Reflection is the return of the signal to the transducer and is used to generate 2D

images; it is greatest when the beam is perpendicular to the tissue. Scatter is the radiation of ultrasound signals in multiple directions from a small structure; the change in frequency of signals scattered from moving blood cells is the basis of Doppler ultrasound. Refraction is deflection of ultrasound waves from a straight path because of differences in impedance, in tissues it can result in double image artefacts. Attenuation is the loss in signal strength due to absorption of ultrasound energy by the tissues, it is frequency dependent with more penetration at higher frequencies. (132-134)

Ultrasound transducers use piezoelectic crystals to generate and receive ultrasound waves. When an electrical current is applied the high frequency changes in voltage can be transformed into mechanical oscillations which is ultrasound. The crystal can also be in receiving mode, if it encounters ultrasound waves, it is distorted. This creates an electrical signal that is analysed by the machine. The crystal can receive if it is not transmitting at that time, therefore it emits a pulse and then listens for a reflection. Each transmitting and receiving period lasts about 1ms. Ultrasound meets many different tissues and echo reflections occur from different depths. Some tissues are more reflective than others such as bone. The echo measures the time delay between transmission of a pulse and reception of a reflection and the intensity of the reflected signal which varies with different tissues. The returning data to the transducer gives information on depth and intensity of reflection, this is electronically converted to a greyscale on the monitor. (132-134)

Echocardiographic planes

There are different positions on the chest wall to obtain different windows of the heart. The standard echocardiograph can give information on the heart chamber size, function (systolic and diastolic), valve motion, masses/fluid collection and direction of blood flow/ hemodynamic information. Several different planes are used to obtain different images of the heart, these are given in Figure 2.1. (134, 135)

1. Long axis plane (corresponds to parasternal long axis images). Used to view the left atrium (LA), left ventricular outflow tract, aorta and ascending aorta.
2. Short axis plane (corresponds to parasternal short axis images). Used to view the left ventricle (LV)
3. Apical plane. Used to obtain two, three, four and five chamber views to view the LV, mitral valve, LA, RV and tricuspid valve.

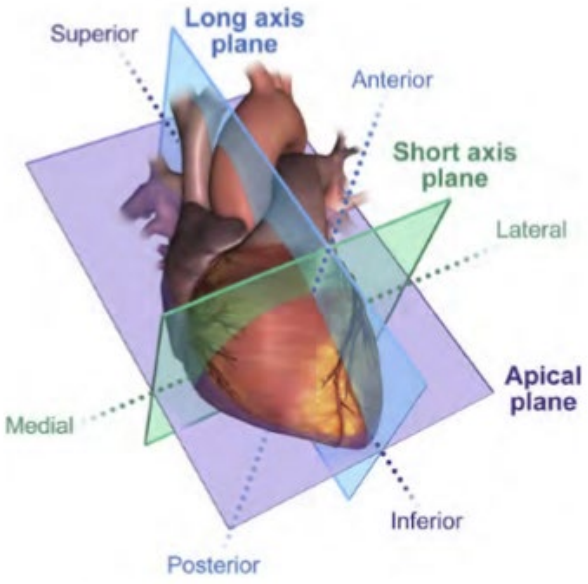


Figure 2.1. Echocardiographic planes of the heart. Reproduced with permission from the American Society of Echocardiography. (135)

Echocardiography techniques

- Two-dimensional (2D) or cross-sectional images.
    - Used to assess anatomy and for positioning for M-mode and Doppler echocardiography. It is also used to view ventricular and value movement.
- Motion or M-mode
    - Used for the measurement of dimensions and timing of cardiac events.
- Pulsed wave Doppler
    - Used for assessment of LV diastolic function and for measurements needed to calculate stroke volume and cardiac output. It is also used to assess valve flow patterns.
- Continuous wave Doppler
    - Used to assess valvular stenosis and regurgitation.
- Tissue Doppler imaging
    - Used for assessment of LV diastolic function.

Two-dimensional echocardiography

This gives a snapshot in time of a cross-section of tissue. When they are produced in quick succession they appear as real time imaging. A three second loop is stored and then later

reviewed offline where it can be frozen at the appropriate time in the cardiac cycle for measurement. (134)

Motion or M-mode echocardiography

This image is produced by the transmission and receipt of an ultrasound signal along one line only giving a higher sensitivity than 2D echocardiography for recording moving structures. The ultrasound signal is aligned perpendicular to the structure being examined. Repeated pulse transmission and receive cycles allow rapid updating of the amplitude vs depth information so that fast moving structures can be identified. The amplitude signal is converted to grey scale with time on the horizontal axis. It produces a graph of changes in movement and time which allows assessment of structures at different times in the cardiac cycle. Images are stored and offline measurements can be made to assess the size and thickness of structures. (132, 134)

Doppler echocardiography

Doppler echocardiography is based on the change in frequency of the backscattered signal from blood cells encountered by the ultrasound beam. This uses moving blood cells to create ultrasound reflections and obtain information on velocity. The ultrasound beam is aligned parallel to the direction of blood flow. A moving object will backscatter ultrasound to the transducer so the frequency when the object is moving toward the transducer is higher and the frequency when moving away is lower. The difference between the transmitted signal and the scattered signal is the Doppler shift. The ultrasound system displays the velocity which is calculated using the Doppler equation, based on transducer frequency and the Doppler shift. (132, 134)

Pulsed wave (PW) Doppler

This allows the velocity of a small area or specific depth to be measured. The 3mm sample volume is placed at the area of interest. A single crystal is used and a pulse of ultrasound is transmitted and then after a time interval; determined by depth, the transducer samples the backscattered signal. This specific site measurement can be used to assess LV inflow and outflow velocities. (132, 134)

Continuous wave (CW) Doppler

Two crystals are used, one transmitting continuously and one receiving continuously from the entire length of the ultrasound beam. This is used to measure high velocities however cannot localise a specific area of interest. (132, 134)

Tissue Doppler imaging (TDI)

The Doppler principle is also used to assess of the motion of the myocardium. The velocity if the movement of the myocardial walls is obtained. The sample volume is placed at specific site in the myocardium and velocities towards and away from the transducer are converted to a spectral display. TDI velocities are less dependant on preload and are used in addition to transmitral flow for assessment of diastolic function. (132, 134)

Echocardiography uses

Cardiac geometry

2D and M-mode images are used for measurements of geometry. Assessment of geometry includes measurement of the LA, interventricular septum, LV end diastolic diameter (LVEDD), posterior wall diameter (PWD), aorta, and ascending aorta. From the measurements, LV relative wall thickness (RWT) and mass can be calculated. Measurements are adjusted for body surface area. (135)

Systolic function

There are different methods for assessing systolic function and calculating EF. Fractional shortening is the percentage change in LV internal dimensions between systole and diastole. (20) Another method is M-mode images or linear measurements to obtain dimensions however, the European and American guidelines note that using volumes rather than linear measurements may be more accurate. (135, 136) They recommend the biplane summation of discs method. This involves using apical images to assess the LV function by viewing the LV in different planes. Left ventricle volumes are estimated from images at the end of diastole and the end of systole; from these volumes the ejection fraction (EF) can be calculated. (20, 135, 136)

Long axis function

Ventricular systole involves longitudinal and circumferential shortening. During systole, long axis function has a major role in changing LV cavity shape and maintaining normal EF. For the right heart, it can give an indication of right systolic function which is difficult to ascertain from 2D echocardiography. The LV and RV long axis spans from the apex to the base of the heart which is usually the mitral and tricuspid valve rings. The ventricles undergo coordinated movements which include shortening of the longitudinal axis, reduction in intracavity diameter and rotation. The base of the heart moves towards the apex during systole. Using M-mode the movement a single point can be tracked through the cardiac cycle. Mitral annular plane systolic excursion (MAPSE) is used to measure long axis function of the left heart. This measurement is taken at the lateral and septal mitral annulus. On the right side, tricuspid annular plane systolic excursion (TAPSE) is measured from the lateral aspect of the tricuspid valve, Figure 2.2 gives MAPSE and TAPSE measurements. (41, 135)

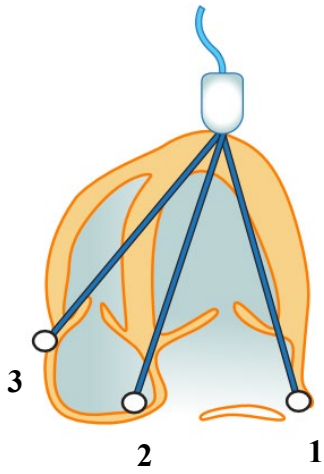


Figure 2.2. Long axis function. M-mode study of movement of the atrioventricular rings towards the apex. Adapted from Kaddoura S. (41)

1. LV free wall (use to measure lateral MAPSE)
2. Intraventricular septum (use to measure septal MAPSE)
3. RV free wall (use to measure TAPSE)

Diastolic function

Diastolic function of the LV is determined by chamber stiffness and relaxation following ventricular contraction. There are several parameters to diagnose diastolic dysfunction and assessment can be complex.

Diastole has four phases

- Isovolumetric relaxation. This begins at the end of systole, there is active and passive LV relaxation determined by compliance.

- Early rapid filling. This is when the LV pressure falls below the LA pressure as a result the LV volume rapidly increases. This is the majority of LV filling, around 70-85%. This corresponds to mitral E-wave on Doppler.
- Late reduced filling. This is when the LV and LA pressure equalise, flow into the LV slows as the pressure difference falls.
- Atrial systole. The LV filling increases and is accounts for 15-20% of LV volume. This corresponds to mitral A-wave on Doppler.

LV diastolic function can be affected by age, preload, afterload and heart rate. Pulsed wave Doppler can be used to obtain transmitral flow velocities. In the normal heart the E-wave of passive filling is greater than the A- wave of active late filling. The pattern of filling can be used to assess function (Figure 2.3). (137)

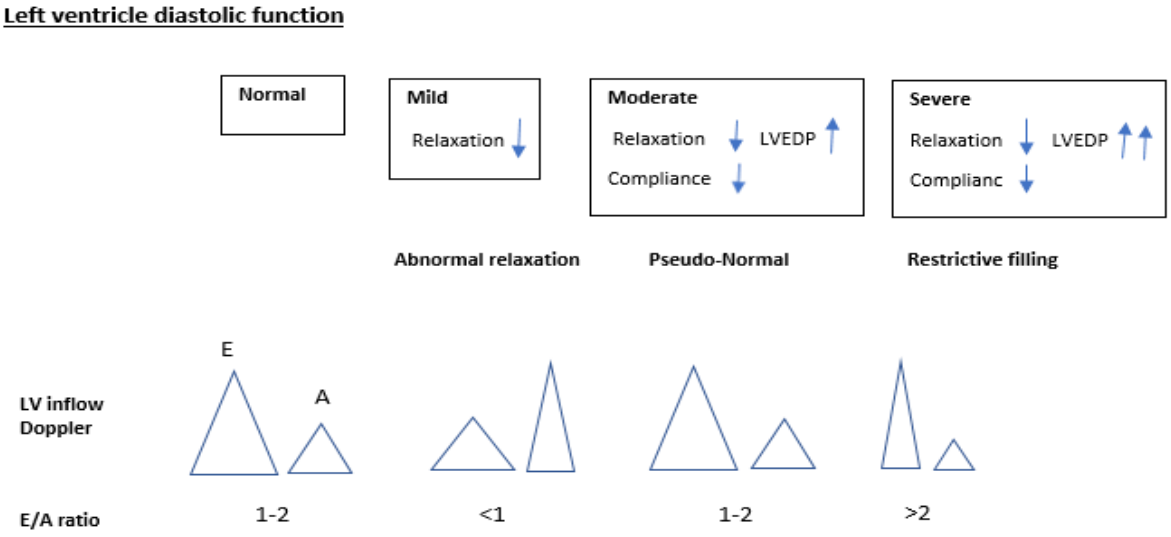


Figure 2.3. Left ventricle diastolic function as assessed by mitral inflow E/A ratio. *LVEDP*, left ventricle end diastolic pressure, *E/A ratio*, mitral inflow E-wave/A wave. Adapted from the British Echocardiographic Society. (138)

Tissue Doppler imaging is another tool for assessment of diastolic function, it can assess the motion of the myocardium. The cardiac cycle can be divided into time intervals, filling and ejection. During ejection there is a positive systolic myocardial wave towards the transducer (S'), whereas during the early filling (E') and late active filling (A') pattern is inverted. The sample volume is placed at the base of the myocardium and signals may be recorded from the basal septum (normal E'>8cm/s) or basal lateral wall (normal >10cm/s). The transmitral flow velocity, E, divided by E' gives the E/E´ ratio. In normal individuals the E/E´ ratio is <8, in

the presence of diastolic dysfunction or impaired relaxation it may be lower and higher values (>13) may indicate elevated filling pressure. (137)

Left atrial volume is another indicator of diastolic function where an increased volume indicates raised LA pressure (normal <34 mL/m^2). Changes in LA volume and pressure can impact pulmonary venous flow which can be assessed by pulsed wave Doppler. The diagnosis of diastolic dysfunction is based on complex criteria using the following groups of measurements LA volume, TDI, transmitral flow and pulmonary venous flow. (137)

Maternal cardiac geometry and function

As mentioned above, subjects were studied by two-dimensional and Doppler trans-thoracic echocardiography using the iE33 Ultrasound System (Philips Ultrasound, USA) equipped with a S5-1 transducer (frequency 1-5MHz). The Guidelines from the European Association of Cardiovascular Imaging, British Society of Echocardiography and American Society of Echocardiography were used to obtain appropriate images. (135, 136, 139) Women were studied after a rest period of 10 minutes in the left lateral decubitus position. Three electrodes were attached to obtain an ECG trace. Standard parasternal and apical views were used and digital loops of 3 cardiac cycles with associated electrocardiogram information were stored on to the hard disk of the machine for offline analysis according to guidelines. The images were taken and analysed by two investigators. When performing the off-line analysis the investigators were blinded for patient group. Table 2.1 gives the measurements taken to assess haemodynamic function, cardiac geometry, systolic, diastolic and longitudinal function.

Table 2.1. Measurements taken at each research clinic visit

	Measurement
Hemodynamic	Systolic blood pressure (mmHg)
	Diastolic blood pressure (mmHg)
	Mean arterial pressure (mmHg)
	Heart rate (beats per minute)
	Stroke volume (ml)
	Cardiac output (ml)
	Total peripheral resistance (dynes/s per cm^5)
	Stroke volume index (ml/m^2)
	Cardiac output index (ml/m^2)

Geometry	Left atrium (cm)
	Left atrium index (ml/m^2)
	Aorta (mm)
	Ascending aorta (mm)
	Left ventricular outflow tract (mm)
	Intraventricular septum (mm)
	Left ventricle end-diastolic diameter (mm)
	Left ventricle end-diastolic diameter index (ml/m^2)
	Posterior wall (mm)
	Relative wall thickness
	Left ventricular mass (g)
	Left ventricular mass index (g/m^2)
Systolic function	End-diastolic volume (ml)
	End-diastolic volume index (ml/m^2)
	End-systolic volume (ml)
	End-systolic volume index (ml/m^2)
	Ejection fraction (%)
	Tissue doppler imaging S’
	Global longitudinal strain (GLS)
	Global circumferential strain (GCS)
Diastolic function	E velocity (m/s)
	A velocity (m/s)
	E/A ratio
	E’ lateral (cm/s)
	E’ medial (cm/s)
	E/E’ ratio
	Left atrial volume (ml)
	Left atrial volume index (ml/m^2)
Longitudinal function	Mitral annular plane systolic excursion- Septal (cm)
	Mitral annular plane systolic excursion-Lateral (cm)
	Tricuspid annular plane systolic excursion (cm)

Echocardiography image acquisition and assessment

Long axis parasternal view

The parasternal long axis (PLAX) allows view of the LV, interventricular septum (IVS), RV, LA and aorta. With the patient in the left lateral decubitus position, the transducer was placed in the third or fourth intercostal space to the left of the sternum with the index marker pointed to the patient's right shoulder (Figure 2.4). If the ventricle did not appear relatively horizontal, the transducer was adjusted by rotating, tilting and/or angling to maximize the LV cavity length within the field of view. (135)

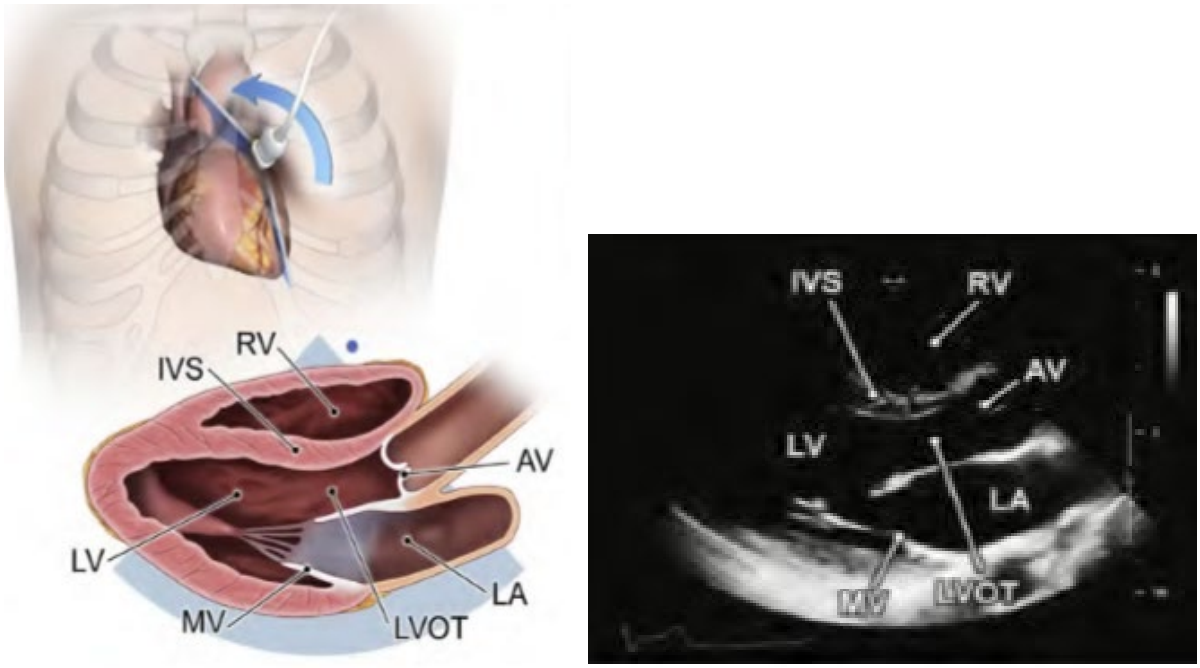


Figure 2.4. Parasternal long axis view. Reproduced with permission from the American Society of Echocardiography. (135)

- Left atrium and aorta

The PLAX image was adjusted to optimise view of the aorta and LA. The cursor was oriented perpendicular to the aortic root and left atrium, at the level of the aortic sinuses. M-mode setting was used to record the image for offline measurement. The LA was measured at the end of systole, the calliper was positioned at the leading edge of the posterior wall of the aortic sinus and extended to the leading edge of the posterior LA wall. In diastole the aorta was measured from the leading edge of the posterior wall of the septum to the leading edge of the posterior wall of the aorta. (135)

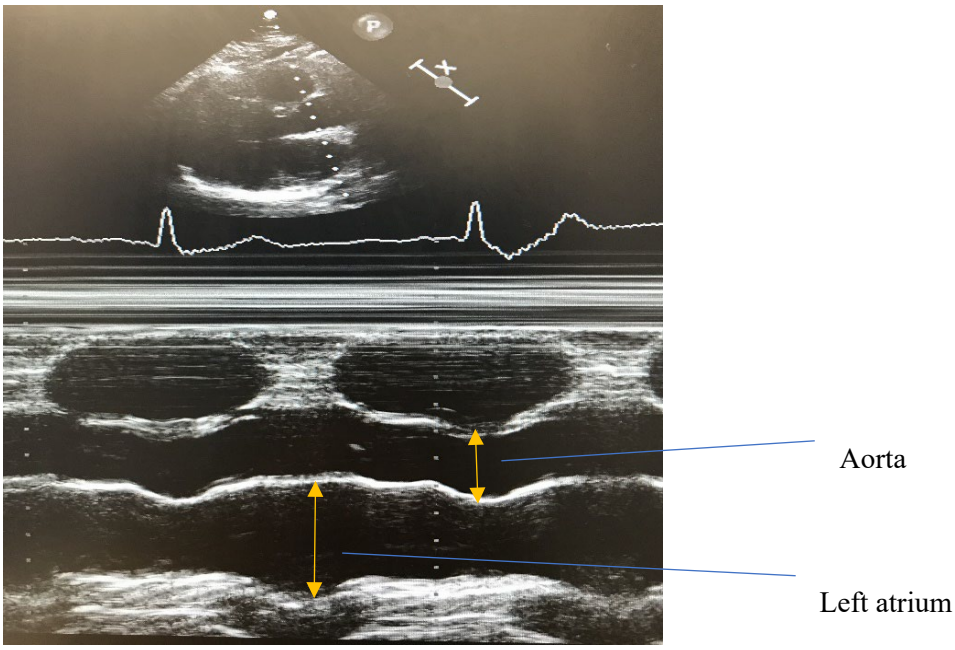


Figure 2.5. M-mode image of the aorta and left atrium

- Ascending aorta

Using the PLAX view the tubular portion of the ascending aorta was measured at the largest dimension identified above the aortic sinuses. (135)

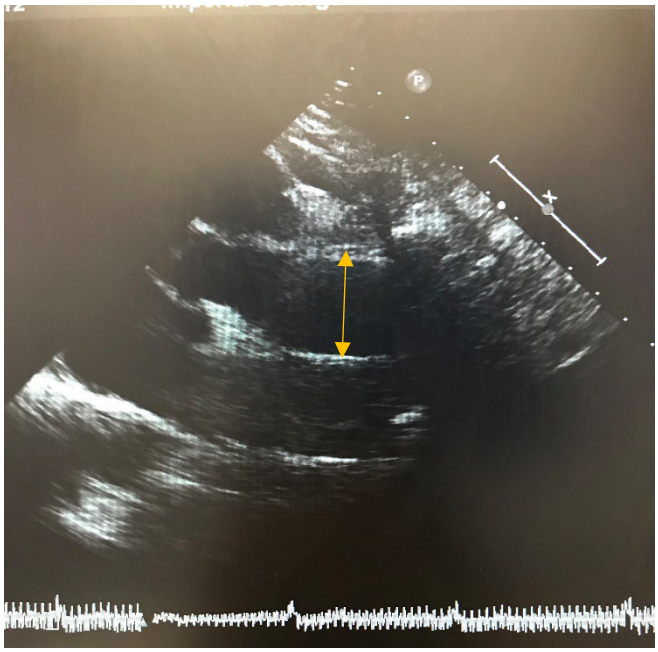


Figure 2.6. Parasternal long axis view of the ascending aorta

- Left ventricular outflow tract

The left ventricular outflow tract (LVOT) was measured from zoomed PLAX images of the LVOT and aortic valve. The image was optimized to show the centre axis of the LVOT with

visualization of the aortic valve cusp insertion points (annulus). Measurements were made from inner edge–to–inner edge, approximately 3 to 10mm from the valve plane in mid systole. (135)

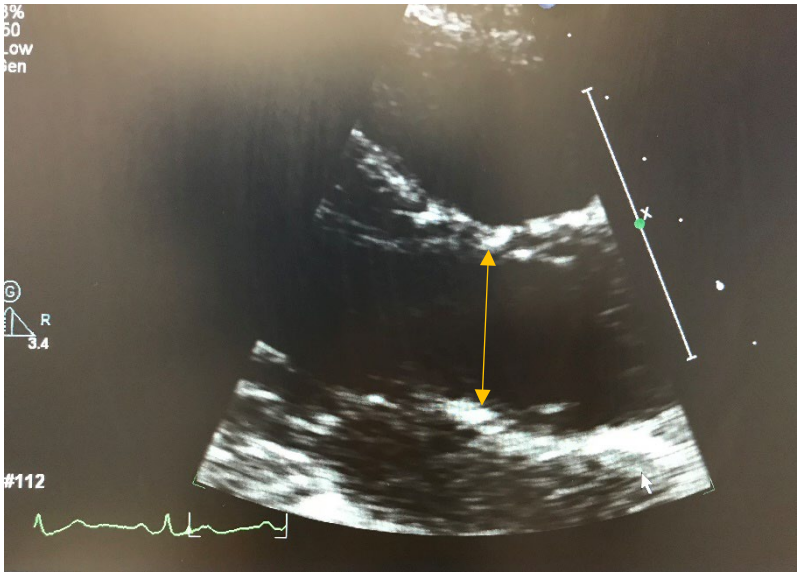


Figure 2.7. Parasternal long axis view of the left ventricular outflow tract diameter

Parasternal short axis view

The parasternal short axis view (PSAX) views were obtained by rotating the transducer 90 degrees clockwise from the PLAX view to position the beam perpendicular to the long axis of the left ventricle. The transducer was tilted superiorly and inferiorly to view different levels. (135)

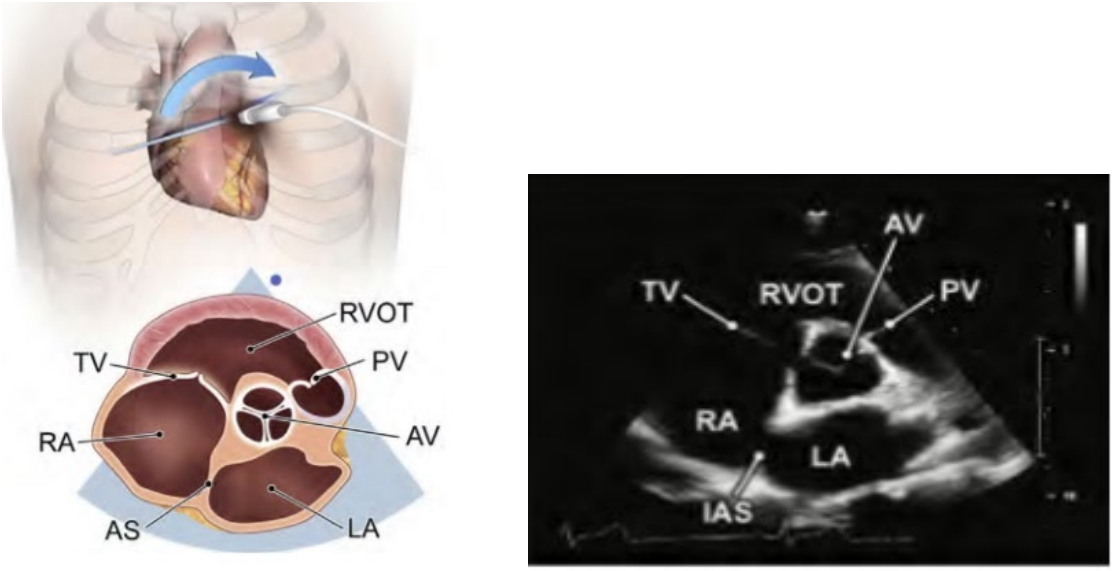


Figure 2.8. Parasternal short axis view. Reproduced with permission from the American Society of Echocardiography. (135)

- Mitral valve

From the level of the great vessels, the transducer was tilted inferiorly and slightly leftward toward the apex of the heart to find the level of the mitral valve. In this view, maximum excursion of both the anterior and posterior leaflets of the mitral value was obtained. (135)

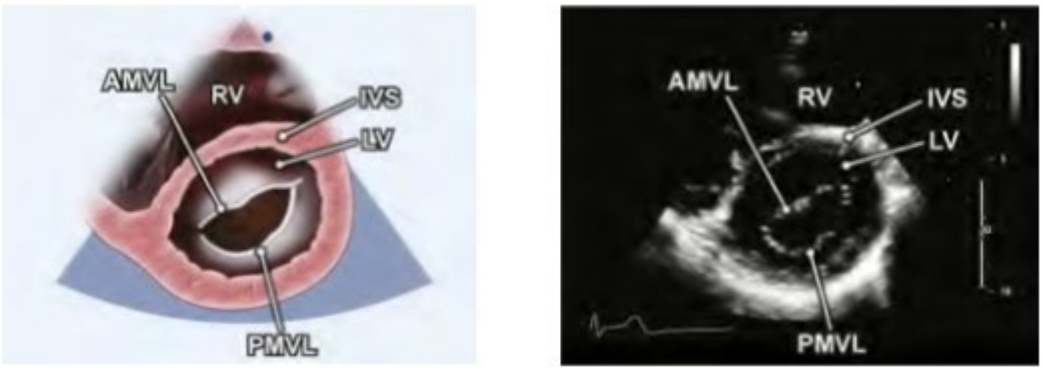


Figure 2.9. Parasternal short axis view of the left ventricle at the level of the mitral value. Reproduced with permission from the American Society of Echocardiography. (135)

- Left ventricle

To obtain the mid LV level, the transducer was tilted just inferior to the tips of the mitral leaflets, at the level of the papillary muscles. Here the ventricle appeared at maximum diameter and circular. The M-mode line was placed perpendicular to the walls of the left ventricle and the image recorded. Offline, the IVS, LVEDD and posterior wall thickness were measured at the end of diastole where the ventricle is the largest. For measurement of the IVS, the calliper was placed at the interface where the RV cavity meets the compacted IVS and moved to where the IVS meets the LV cavity. For measurement of the LV internal diameter, the calliper was placed at the interface of the compacted myocardium of the IVS and a line extended perpendicular to the long axis of the LV to the inner border of the compacted myocardium of the posterior wall. For measurement of the LV posterior wall, the calliper was placed at the interface of the compacted posterior wall and LV cavity and moved to the LV posterior wall-pericardial interface (Figure 2.10 and 2.11). (135, 136)

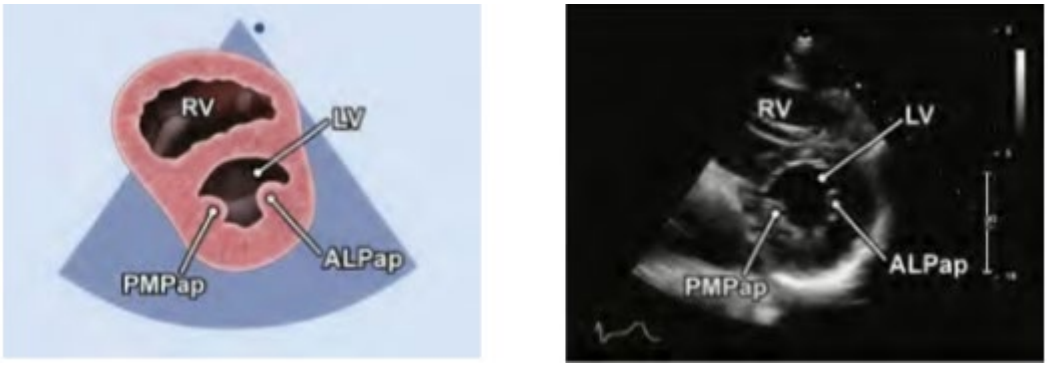


Figure 2.10. Parasternal short axis view of the left ventricle at the level of the papillary muscle. Reproduced with permission from the American Society of Echocardiography. (135)

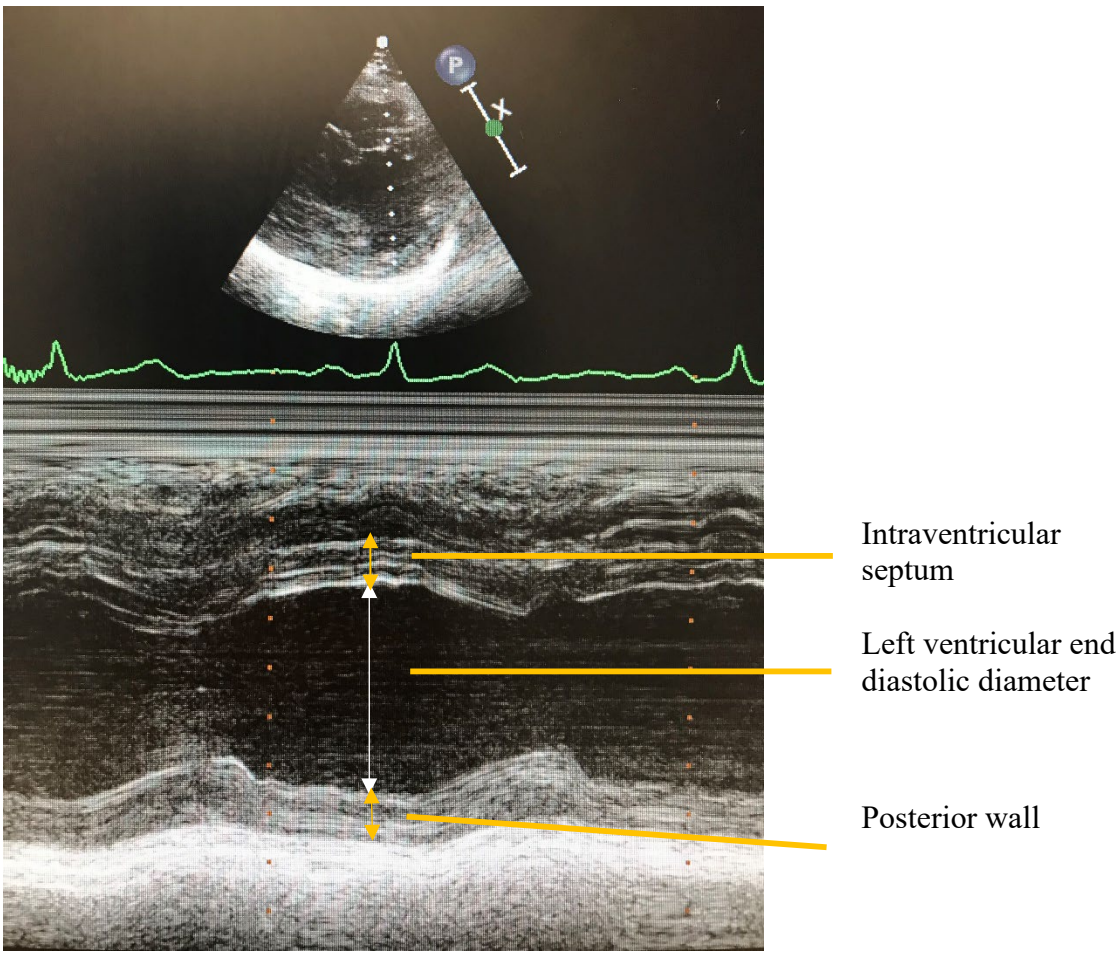


Figure 2.11. M-mode tracing of the left ventricle. Measurement of the interventricular septum, left ventricle diameter and posterior wall thickness, all at end-diastole.

The apical third of the ventricle was viewed by tilting the transducer or sliding the transducer down one or two rib interspaces and laterally to best see the apex. (135)

Figure 2.12. Parasternal long axis view of the left ventricle at the level of the apex. Reproduced with permission from the American Society of Echocardiography. (135)

Apical Views

The apical plane allows view of the LV, LA, RV and right atrium (RA). The apical position was obtained from the left side of the chest in the fifth intercostal space in the midaxillary line. To obtain the apical four chamber view the transducer was placed at the palpated apical pulse with the index marker pointing towards the bed. The apex of the left ventricle is at the top and centre of the sector with the right ventricle considerably smaller. (135)

Figure 2.13. Apical four chamber view. Reproduced with permission from the American Society of Echocardiography. (135)

- Left ventricular inflow

Pulsed wave Doppler was used to assess the patterns of forward diastolic flow across the mitral valve (MV). The apical four chamber view was adjusted to focus on the MV which was positioned in the centre of the sector. The sample volume of the pulsed wave Doppler was placed at the tips of the open MV leaflets and the image recorded. The measurement was taken by placing a calliper at the peak of the E and A velocities. (135)

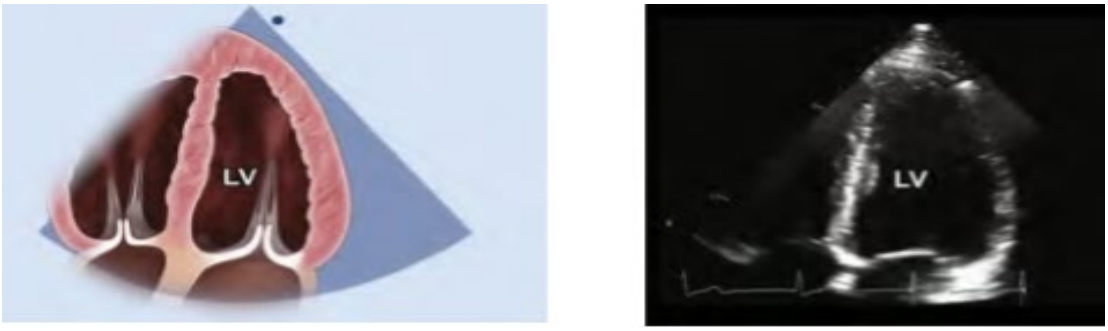


Figure 2.14. Apical four chamber view focused on the left ventricle and mitral value. Reproduced with permission from the American Society of Echocardiography. (135)

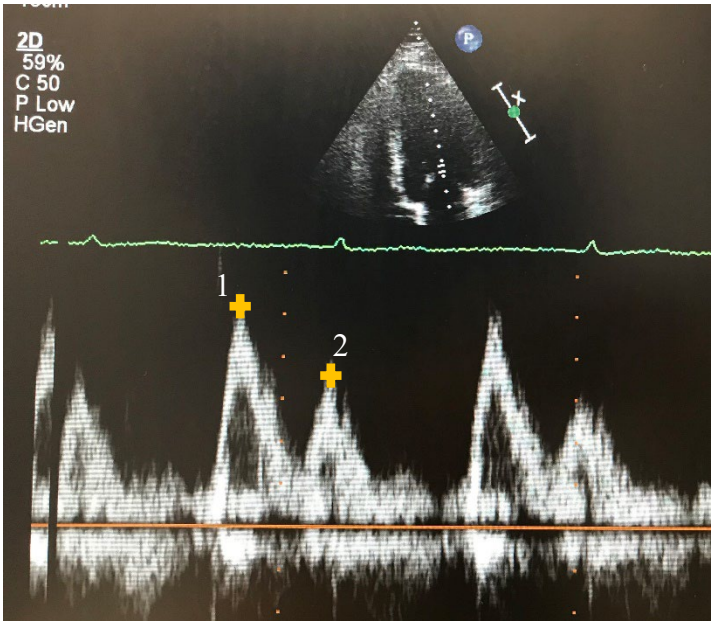


Figure 2.15. 1. E-wave velocity 2. A-wave velocity, used to calculate the E/A ratio

Tissue Doppler imaging of the Mitral and Tricuspid Annuli

Using the apical four chamber view, tissue Doppler imaging was used to record velocities of the longitudinal motion of the lateral and medial mitral annulus and lateral tricuspid annulus. (135)

- Mitral annulus

Using the tissue Doppler imaging setting, the sample volume was placed within 1cm of the insertion of the mitral value leaflets laterally and medially. The velocity waveform image was recorded for offline analysis. Callipers were used to record the value for E' lateral and E' medial, these values were averaged. The E/E' ratio was calculated by dividing the Pulsed wave Doppler mitral inflow velocity, E, by the averaged E'. (135)

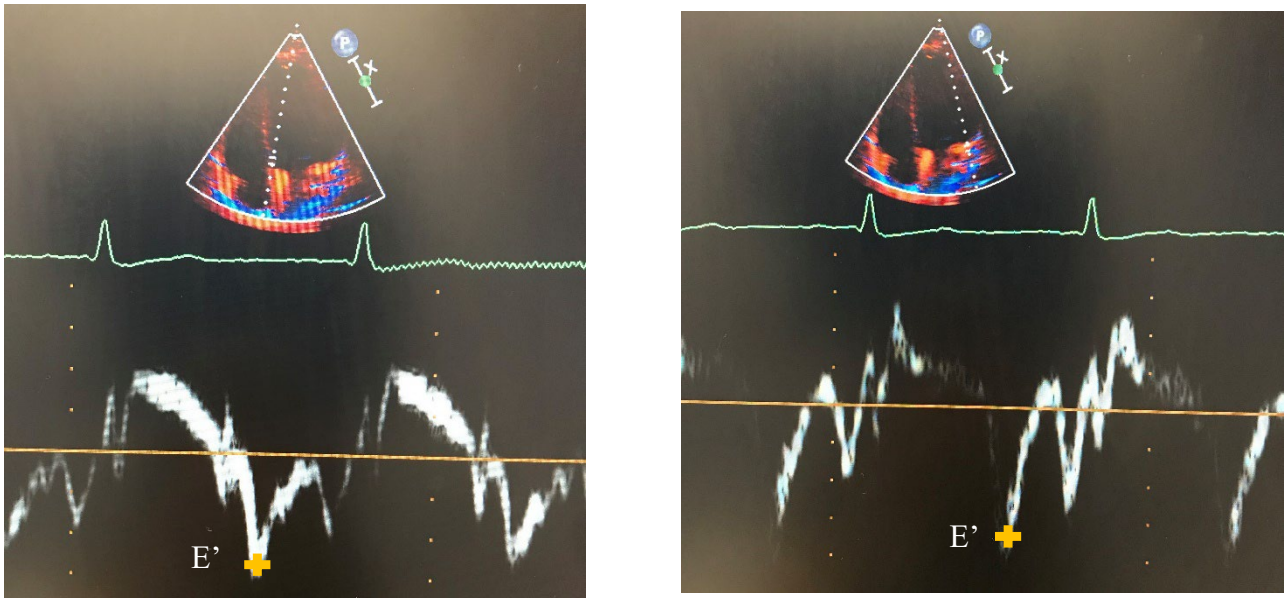


Figure 2.16. Tissue doppler imaging of the mitral annulus, E' medial (left) and E' lateral (right).

- Tricuspid annulus

The apical four chamber view was adjusted to optimise view of the RV and TV. Using the Tissue Doppler imaging setting, the sample volume was placed on the lateral tricuspid annulus. On the velocity wave form image, a calliper was used to record the value for S'. (135)

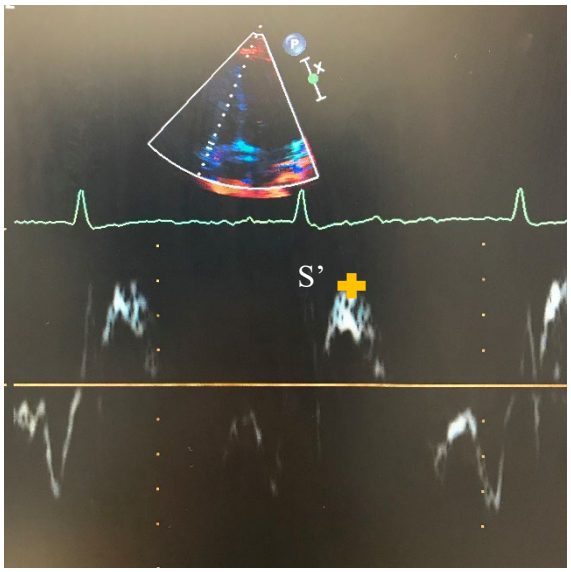


Figure 2.17. Tissue doppler imaging of the lateral tricuspid annulus S'

- Tricuspid annular plane excursion

The apical four chamber view was adjusted to focus on the right ventricle. The M-mode cursor was aligned along the RV wall parallel to the movement and perpendicular to the tricuspid value annulus. On the M-mode image the distance from the annulus towards the apex is measured from the end of diastole to the end of systole. (135)

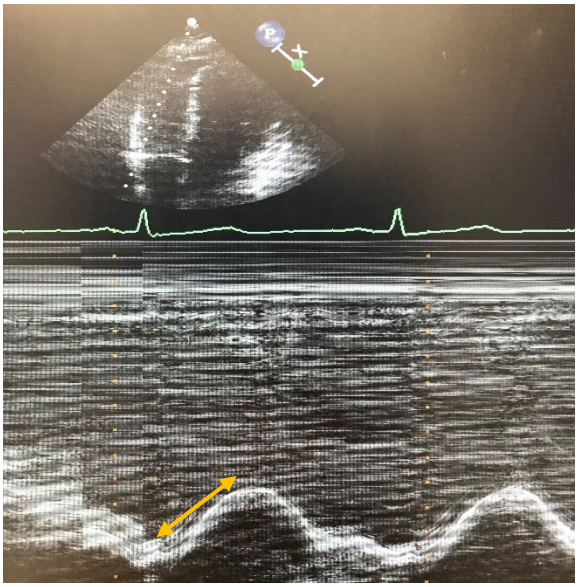


Figure 2.18. Tricuspid annular plane systolic excursion measured by M-mode showing movement of the tricuspid valve ring towards the apex

- Mitral annular plane systolic excursion

The apical four chamber view was adjusted to focus on the LV. The M-mode cursor was aligned along the LV lateral wall parallel to the movement and perpendicular to the mitral value annulus. On the M-mode image the distance of the annulus towards the apex is measured from the end of diastole to the end systole. This was repeated with the M-mode cursor aligned along the septum, parallel to the movement and perpendicular to the medial mitral annulus. (41, 140)

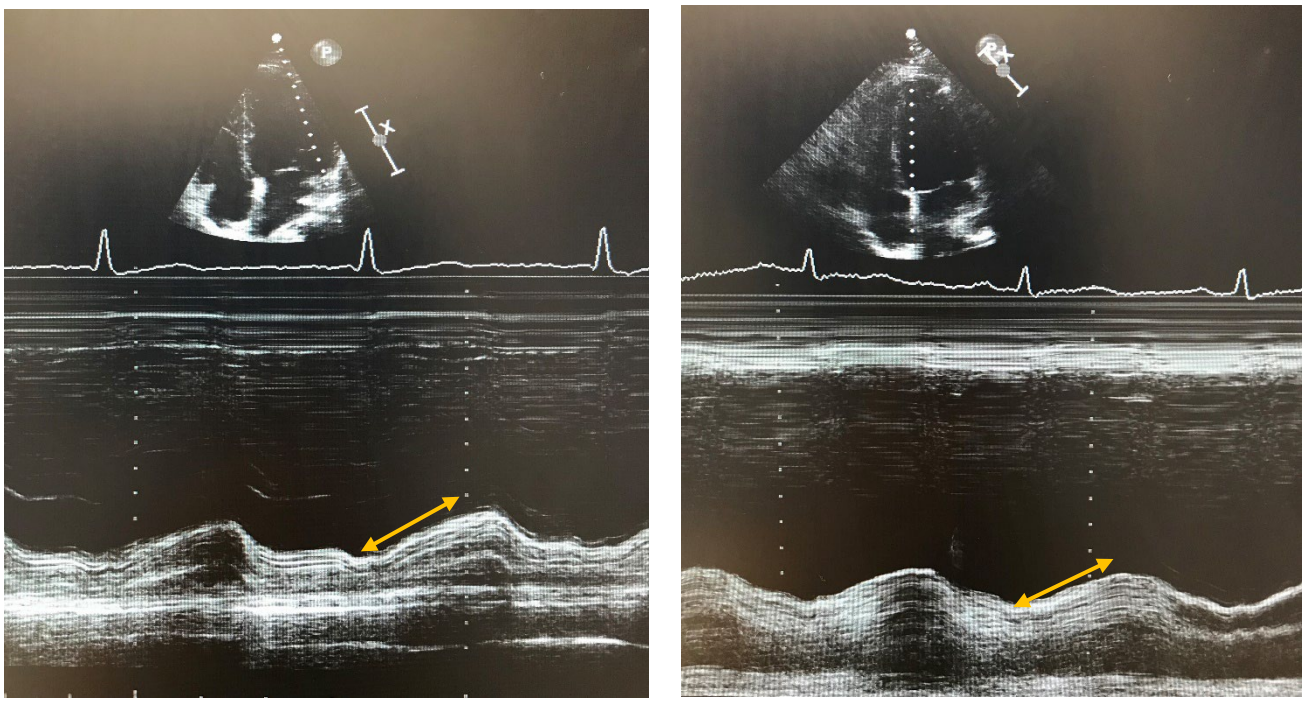


Figure 2.19. Mitral annular plane systolic excursion lateral (left) and septal (right)

- Left atrium volume

The apical four chamber view was adjusted to focus on the LA. The largest appearing image at the end-systole was used for the measurement. The endocardial border was traced by drawing a line from one aspect of the annulus to the opposite side. Following this the length of the atrium was measured by starting at the centre point of the annulus to the furthest point of the tracing. The machine then calculated the volume. LA volume was measured only in the four chamber view as the two chamber view images were of inadequate quality. (135)

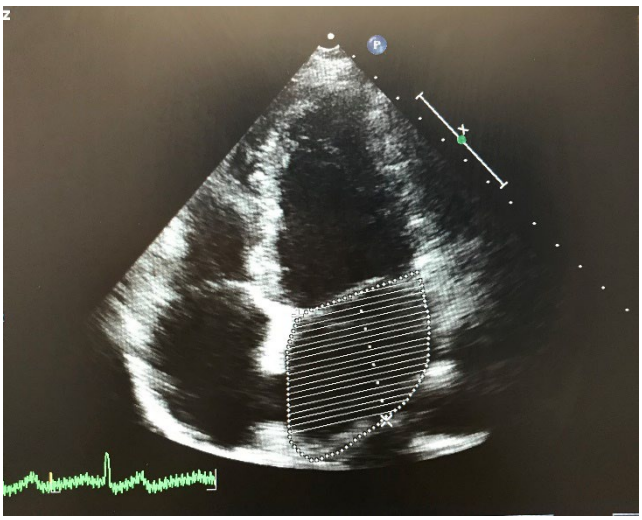


Figure 2.20. Apical four chamber view of left atrial volume

- Left ventricle volume

The biplane disc summation method uses apical four chamber and two chamber views. The apical four chamber view was obtained and then adjusted to focus on the left ventricle with the apex in the centre and the long axis of the ventricle maximised. The sector width was reduced to include just the LV and MV in order to maximise frame rate for enhanced definition. The recorded clip was stopped at the end of diastole and the measurement was taken using this image. A line was drawn horizontally across the left ventricle at the level of the MV annulus. Following this the LV cavity was traced along the interface of the compacted and noncompacted myocardium of the chamber wall. The machine then calculated the LV volume. The clip was then moved forward to the image at the end of systole. Again, a line was drawn horizontally across the LV at the level of the mitral valve annulus and then the LV cavity was traced; the machine then calculated the LV volume. The biplane method repeats this process of measuring the LV volume at end-diastole and end-systole in the two chamber view. To move from the apical four chamber view to the two chamber view the transducer was rotated approximately 60 degrees in an anticlockwise direction until only the LV and LA were in view. Using the values for the end-diastolic volume and end-systolic volume in both the two and four chamber view, the ejection fraction was calculated by the machine. (20, 135)

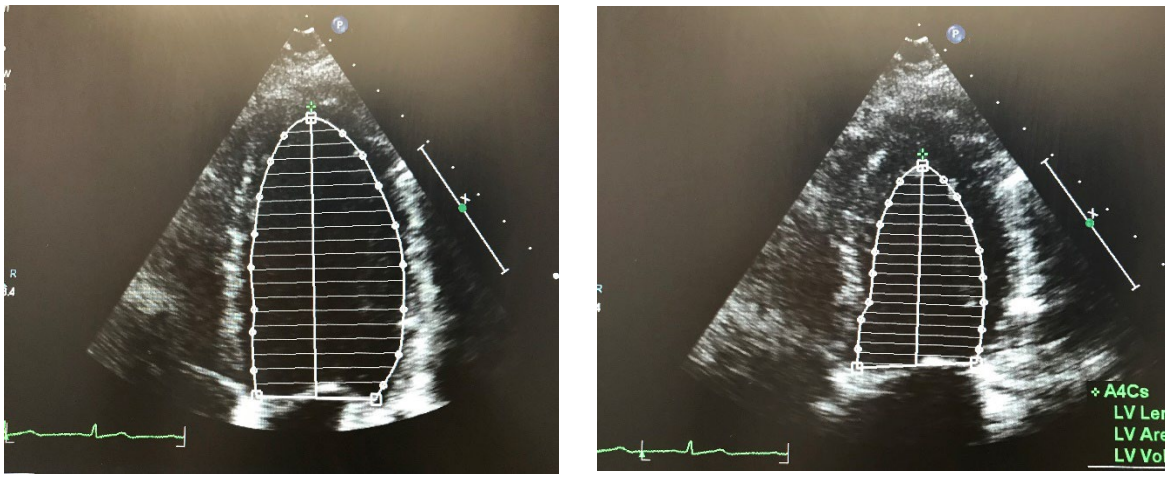


Figure 2.21. Apical four chamber left ventricular volume in diastole (left) and systole (right)

- Left ventricular out flow tract velocity time integral

The velocity time integral (VTI) is used for calculation of stroke volume and is obtained using the five chamber view. From the apical four chamber view the transducer was tilted anteriorly until the LVOT, MV and aorta were clearly seen. The velocity in the LVOT was measured using the pulsed wave Doppler function. The sample volume was placed 5mm proximal to the

aortic valve in the centre of the LVOT and the image recorded. The area under the curve is the VTI which was manually traced for the machine to calculate the value.(135, 141)

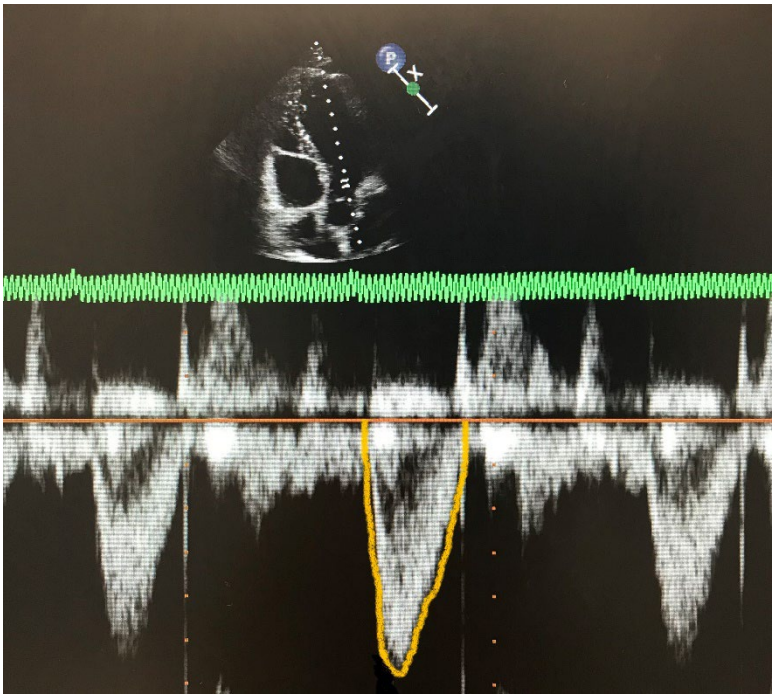


Figure 2.22. Five chamber view, pulsed wave Doppler of left ventricular outflow tract velocity time integral

- Additional view

The three chamber view was required for speckle tracking analysis, it was obtained by starting at the apical four chamber view and rotating the transducer anticlockwise approximately 120 degrees. The apex was seen along with the LA, LVOT and aortic valve. The two, three and four chamber views were used for speckle tracking analysis. (135, 136)

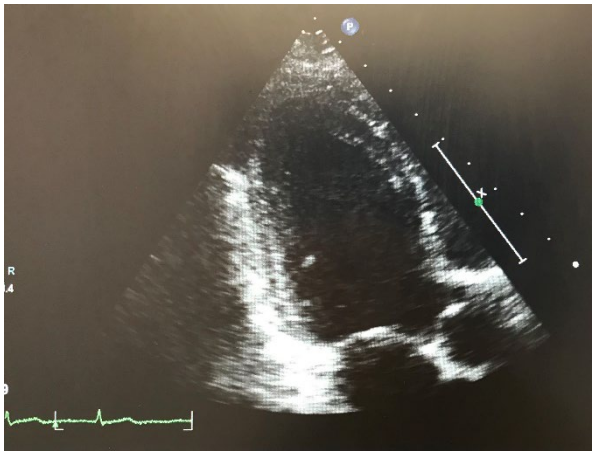


Figure 2.23. Apical three chamber view

Measurements

1. Mean arterial pressure was calculated as Systolic blood pressure + (2 x Diastolic blood pressure)]/3. (33)
2. Cardiac output (ml) calculated as Stroke volume x Heart rate. (141)
3. Stroke volume (ml) calculated as CSA x Velocity time integral. (141)
    - Where CSA is Cross-sectional area of the LV outflow tract
    - $CSA = \pi r^2 = \pi \left(\frac{D}{2}\right)^2 = 3.14D^2/4 = 0.782D^2$ (D=diameter of the LVOT in cm)
    - Stroke volume = VTI x 0.785D
4. Total vascular resistance (dynes/sec per cm^5) calculated as (MAP/CO in L/min) × 80. (33)
5. Left ventricular Mass (g) calculated as (0.8 x (1.04x [$(IVS+LVEDD+PWT)^{3)} - LVEDD^3$]) + 0.6g. (136)
    - Linear method using cube formula
6. Relative wall thickness was calculated as (2 x LVPWd)/ LVEDD. (136)

    - Where LVPWd is LV posterior wall thickness in diastole and LVEDD is LV end diastolic dimension.

7. Body surface area (BSA) calculated as ($W^{0.425}$ x $^{H0.725}$) x 0.007184
    a. DuBois and DuBois formula where the weight is in k and the height is in cm. (142)
8. Birthweight percentiles were calculated using Fetal Medicine Foundation fetal and neonatal population weight charts from the Fetal Medicine Foundation online resources. (131)

Speckle tracking echocardiography

In addition to traditional echocardiography strain imaging was used in a number of participants in order to further assess maternal cardiac function. Strain is a dimensionless measure of myocardial deformation which gives an assessment of myocardial motion and function. It is the fractional change in an object's dimension compared to its original dimension. Strain information can be obtained using either tissue TDI or STE. (21) Speckle tracking echocardiography is based on the motion of acoustic markers (speckles) produced by the interaction of ultrasound with the myocardium, these can be tracked through the cardiac cycle with specific software. The movement of the speckles can be used to calculate strain rate which is the speed at which deformation occurs. Global contraction is assessed via longitudinal and circumferential strain which can give an assessment of global and regional function. This method of assessment of cardiac function has been validated against cardiac MRI and is superior to ejection fraction due to being independent of loading conditions. It also has the ability to detect active contraction rather than the passive motion caused by movement of adjacent tissue. Global longitudinal strain (GLS) has been found to be more sensitive to subclinical changes of LV function since it is a direct measure of myocardial movement. (21, 42, 43) Parasternal short axis views and apical 2, 3 and 4 chamber views were analysed using the 2D Cardiac Performance Analysis, TomTec Imaging System, Munich, Germany. Images were optimised with adequate settings of gain, focus, depth and sector width to reach a frame rate over 60 frames per second. All speckle tracking analysis was performed by the same experienced operator (Dr Olga Patey). The LV endocardial borders were delineated by the software and manually corrected if the software failed to track them precisely throughout the cardiac cycle. Segmental peak systolic strain values were averaged over 2 cardiac cycles. To calculate global longitudinal and circumferential strain (GCS), corresponding segmental values of the standard 16 LV segments were used. (143, 144)

Inter- and Intra- observer reliability

The echocardiographs were performed and analysed by two independent investigators who were blind to the patient allocation during the offline analysis. Investigator 1 had several years of experience performing detailed cardiac echocardiography (Dr Nunzia Borrelli). Investigator 2 is the student submitting the current Thesis. After 9 months of training, the inter-observer

reliability was assessed by calculating the Intraclass Correlation Coefficient (ICC) which evaluates variability of different investigators measurements of the same participant relative to variability between participants. The ICC is measured on a scale of 0 to 1, where 0 indicates no reliability between assessors and 1 indicates complete reliability with no measurement error. Values between 0.5-0.75 indicate moderate reliability, between 0.75 and 0.9 indicate good reliability, and values greater than 0.90 indicate excellent reliability. (145, 146) Two hundred parameters from ten echoes were analysed by both assessors. Table 2.2 gives the ICC for each parameter measured with 95% confidence interval (CI). Overall there was good or excellent reliability across the measurements.

Table 2.2. Interclass correlation coefficient of investigator 1 and 2.

Measurement	ICC
Left atrium diameter	0.891 (0.81-0.923)
Aorta	0.882 (0.8-0.945)
Ascending aorta	0.912 (0.899-0.951)
LV outflow tract	0.938 (0.777-0.984)
Intraventricular septum	0.781 (0.751-0.911)
LV end diastolic diameter	0.895 (0.682-0.974)
Posterior wall thickness	0.781 (0.761-0.911)
End diastolic volume	0.897 (0.688-0.974)
End systolic volume	0.8 (0.711-0.958)
Tissue Doppler imaging s’	0.944 (0.928-0.998)
E velocity	0.942 (0.766-0.986)
A velocity	0.961 (0.844-0.99)
Tissue Doppler imaging E’ lateral	0.955 (0.799-0.989)
Tissue Doppler imaging E’ medial	0.967 (0.848-0.992)
Left atrium volume	0.912 (0.881-0.937)
Tricuspid annular plane systolic excursion	0.93 (0.72-0.983)
Mitral annular plane systolic excursion- septal	0.932 (0.723-0.983)
Mitral annular plane systolic excursion- lateral	0.901 (0.856-0.944)
LV outflow tract velocity time integral	0.951 (0.813-0.988)

Intra-observer reliability of Investigator 2 was also assessed by repeating measurements for 100 parameters from five echocardiographs. Further ICC values were used to assess the repeatability of Investigator 1, these are given in Table 2.3

Table 2.3. Interclass correlation coefficient of investigator 1 with measurements six months apart

Measurement	ICC
Left atrium diameter	0.901 (0.877-0.945)
Aorta	0.911 (0.891-0.967)
Ascending aorta	0.942 (0.899-0.96)
LV outflow tract	0.869 (0.791-0.921)
Intraventricular septum	0.821 (0.799-0.893)
LV end diastolic diameter	0.92 (0.9-0.969)
Posterior wall thickness	0.899 (0.921-0.056)
End diastolic volume	0.89 (0.87-0.969)
End systolic volume	0.91 (0.89-0.981)
Tissue Doppler imaging s'	0.989 (0.97-0.998)
E velocity	0.957 (0.911-0.986)
A velocity	0.966 (0.931-0.989)
Tissue Doppler imaging E' lateral	0.988 (0.965-0.991)
Tissue Doppler imaging E' medial	0.97 (0.955-0.988)
Left atrium volume	0.967 (0.948-0.984)
Tricuspid annular plane systolic excursion	0.987 (0.981-0.993)
Mitral annular plane systolic excursion- septal	0.945 (0.922-0.969)
Mitral annular plane systolic excursion- lateral	0.932 (0.908-0.979)
LV outflow tract velocity time integral	0.902 (0.871-0.948)

Statistical analyses

Corp., Armonk, New York, USA). For continuous data the Kolmogoroff–Smirnoff and Shapiro-Wilk tests were used to assess normality of the distribution. Data were expressed as mean (standard deviation; SD) or as median (interquartile range) for normally and not normally distributed data respectively and as a percentage for categorical variables. The groups were compared using the unpaired Student t-test/Mann-Whitney or chi-square ($\chi 2$) for numerical and categorical data respectively. Differences were considered statistically significant at $p<0.05$. The groups were compared at each time point using median and interquartile range or

mean and standard deviation. Within each group, the time points (trimesters) were compared, the p values for time 1 vs 2, time 1 vs 3 and time 2 vs 3 are given.

Pearson's correlation coefficient (R) was used to evaluate the correlation between parameters described in each chapter. Regression analysis was used to assess whether correlations remained significant after consideration of the influence of maternal characteristics including gestation, maternal age, race and development of GDM (Chapter 6).

Power calculations are described in each results chapter 3,4 and 5. There are no previous studies investigating the cardiovascular system pregnant women with previous bariatric surgery, using studies of individuals before and after bariatric surgery outside of the context of pregnancy we have estimated sample sizes.

Mixed model analysis

Hierarchical modelling was used to further assess differences found by cross sectional analysis using the Student t-test/Mann-Whitney. Non-parametric data was made Gaussian after $\log_{10}$ transformation. Multilevel linear mixed-effects models were performed for the repeated measures analysis with adjustment for maternal BMI, age, race, smoking, gestational age at the time of the examination and development of GDM. (147, 148)

The fixed effect component included time (the 3 visits), study group, BMI, age, race, smoking, gestational age, GDM and first-order interaction between time and study group. The likelihood ratio test was used to determine the best fit multilevel model. The baseline model included fixed effect for time and group and no random effects. Different versions of the model included only the random slope for time or random intercept or both time and random intercept. The likelihood ratio was compared to the baseline model. The model improved when further fixed effects were added (age, BMI, race, GDM, smoking and gestation). The estimated marginal means and p value for group comparison is presented at each time point. Further to this, overall group comparison across all trimesters is presented. The mixed model analysis was performed with assistance from Statistician Dr Sebsatian Nastuta.

Chapter 3

Maternal cardiovascular adaptation in pregnancy in women with previous bariatric surgery compared to women with a similar pre-surgery BMI

Abstract

Background: Obesity in pregnancy is associated with significant risks, notably hypertensive disorders. Studies of the maternal cardiovascular function in obese pregnant women are limited, however, there is evidence of a hyperdynamic circulation with higher cardiac output, diastolic dysfunction and a reduction in global longitudinal strain. Bariatric surgery is a successful treatment for sustainable weight loss and has several cardiovascular implications including improvement or resolution of hypertension, changes in cardiac geometry and improvement in diastolic and systolic function compared to before surgery. Pregnancy after bariatric surgery is associated with a reduced risk of hypertensive disorders. Nevertheless, the maternal cardiovascular system after bariatric surgery has not been previously investigated.

Objective: To investigate the maternal cardiovascular adaptation to pregnancy in women with previous bariatric surgery compared to women with a similar pre-surgery body mass index (BMI) but no history of weight loss surgery.

Methods: This was a prospective, observational, longitudinal study including pregnant women with (n=33) and without (n=33) previous bariatric surgery but similar pre-surgery body mass index BMI, age and race. Participants were seen at three time points; 12-14, 20-24 and 30-32 weeks of pregnancy. At each visit blood pressure (BP) was measured and maternal cardiac geometry and function were assessed using trans-thoracic echocardiography. On a subset of patients (15 in each group), 2D speckle tracking was performed to assess global longitudinal and circumferential strain. Offline analysis was performed according to the European and

American echocardiography guidelines. Multilevel linear mixed-effects models were used for all comparisons.

Results: Haemodynamically the BP, heart rate and cardiac output were lower and peripheral vascular resistance higher in the post-bariatric pregnant women compared to the no-surgery group ($p<0.01$ for all comparisons). Similarly, there were differences in cardiac geometry with lower left ventricular mass and relative wall thickness in the post-bariatric group ($p<0.01$ for both). There was evidence of more favourable diastolic indices with a higher E-wave/ A-wave flow velocity across the mitral valve, higher mitral annular velocity (tissue Doppler imaging) at the lateral and medial annulus (E') and lower left atrial volume in the post-bariatric group ($p<0.01$ for all comparisons). There was no difference in systolic function measured by ejection fraction, however, global longitudinal strain was lower in the post-bariatric group indicating better systolic function ($p<0.01$).

Conclusion: Our findings indicate a better cardiovascular adaptation to pregnancy in women with previous bariatric surgery compared to pregnant women of a similar pre-surgery BMI but no history of surgery. This may explain why women after bariatric surgery are less susceptible to hypertensive disease in pregnancy and could influence national guidance regarding favourable effects of bariatric surgery in obese women of reproductive age.

Introduction

In the UK in 2017 a third of women were obese, many of which were of childbearing age and went on to have high risk pregnancies. (3) Obesity has several effects on the cardiovascular system including a hyperdynamic circulation with raised cardiac output (CO), altered geometry with increased left ventricle (LV) mass and an increased incidence of diastolic dysfunction. (6, 19) Bariatric surgery is the most effective method for inducing long-lasting weight loss. (149) Guidelines recommend bariatric surgery for BMI≥40 or for BMI=35-40 with comorbidities such as diabetes or hypertension. (78, 81) Studies investigating the effect of bariatric study on the cardiovascular system, outside pregnancy, have found that surgery is associated with an improvement or resolution of hypertension, changes in cardiac geometry including reduction in LV mass and improvement in diastolic function compared to before surgery. (10, 87, 91) Haemodynamically, there is reduction in heart rate (HR) and CO similar to that of a normal BMI group.(102, 106) Systolic function measured by ejection fraction (EF) is unchanged or

mildly improved however, some studies have shown global longitudinal strain is significantly improved after bariatric surgery. (103, 108, 150)

Normal pregnancy is associated with significant maternal cardiovascular and haemodynamic changes that are needed to adapt to a physiological volume overload state. Systemic vasodilation leads to a reduction in resistance and an increase in stroke volume (SV) and CO. (28) Typically, EF is preserved however, there is evidence of a tendency towards reduced diastolic reserve. (37) In recent years maternal cardiovascular adaptation to pregnancy has been implicated in the pathophysiology of placenta-related pregnancy complications such as pre-eclampsia (PE) and/or fetal growth restriction (FGR). (45) Studies have associated late PE with a high maternal CO and low resistance, however, more recently it has been reported that early and late PE are both related to hyperdynamic circulation. (55, 56) In addition to hemodynamic changes, maternal LV hypertrophy and reduced diastolic indices have been shown to be present in hypertensive pregnancies. (54) Although the results are inconsistent, it is evident that the traditional hypothesis of a placental related disease now has a maternal cardiovascular focus.

Obesity in pregnancy is associated with significant maternal and fetal risks including increased risk of gestational diabetes, hypertensive disorders, venous thromboembolism and macrosomia. (60) There are a limited number of studies investigating the effect of obesity on the maternal cardiovascular system; small studies have found an increase in LV mass, however, no change in function. (70, 71) Conversely, another study found that 40% of morbidly obese pregnant women have diastolic dysfunction together with a significant reduction in global longitudinal strain, a sensitive marker of systolic function, compared to women with a BMI<30. (72) A longitudinal study of obese pregnant women found a high volume/low-resistance circulation in the first and second trimester, however, in the third trimester, the CO of obese women decreased which was not true in non-obese women; they conclude that there is a shift towards volume overload and a disappearance of previously seen low resistance. (74) These differences suggest a maladaptive cardiovascular response to pregnancy.

Several studies have demonstrated that pregnancy following bariatric surgery is associated with a reduced risk of gestational diabetes (GDM), delivery of large for gestational age neonates and notably, hypertensive disorders but increased risk of small-for-gestational age neonates, compared to pregnancies of women with similar pre-surgery BMI. (111) Despite the fact that maternal cardiovascular adaptation to pregnancy plays a pivotal role in maintaining a healthy pregnancy and maladaptation has been associated with hypertensive disease and FGR, there

are no studies investigating the maternal cardiovascular adaptation to pregnancy of women with previous bariatric surgery.

Hypothesis

In pregnancies following bariatric surgery, maternal cardiovascular adaptation is altered compared to that of women with similar pre-surgery BMI.

Aim

1. Investigate longitudinally, the maternal cardiovascular adaptation to pregnancy in women following bariatric surgery compared to pregnant women with early pregnancy BMI similar to the pre-surgery BMI of the post-bariatric surgery women.
2. Investigate the association of maternal haemodynamic indices with birth weight.

Methods

This was a prospective, observational, longitudinal study. Pregnant women were recruited from April 2018 to June 2020 at Chelsea & Westminster Hospital, London, UK. Participants were identified through a booking-perinatal database (CIMIS). Following the 1st trimester scan, participants were approached by members of the research team and recruited in the following groups:

- Group 1 – Pregnant women with previous bariatric surgery
- Group 2 – Pregnant women without a history of bariatric surgery matched for pre-surgery BMI, age, race and presence of diabetes

Women who had a singleton pregnancy and attended at least two out of three research visits were included. Participants were seen at three time points during their pregnancy, 12-14, 20-24 and 30-32 weeks. Women who had bariatric surgery were matched to women without surgery. Matching between the groups was achieved via categories for BMI (20-24.9, 25-29.9, 30-34.9, 35.0-39.9, ≥40), age (20-25, 26-30, 31-35, 25-40, >40), race (white or non-white) and presence of diabetes mellitus.

Maternal characteristics, including age, parity, race, smoking status and medication history were recorded in the research database. Maternal weight was taken to the nearest 0.1 kg using a calibrated electronic scale, with the patient wearing light clothing and no footwear. Height was measured to the nearest 0.5 cm also without footwear. Blood pressure (BP) measurements were performed manually using a sphygmomanometer (Accoson Dekamet, AC Cossor & Son (Surgical) Ltd, London, UK) according to the recommendations of the British Hypertension Society. (120) Two readings, 5 minutes apart, were taken in a seated position from the left arm. The mean value was recorded. Maternal cardiovascular system was assessed using 2D echocardiography and cardiac geometry, haemodynamic variables, systolic, diastolic and longitudinal function were evaluated.

Transthoracic echocardiography was performed after a rest period of 10 minutes in the left lateral decubitus position. Two-dimensional, M-mode and tissue Doppler imaging were performed using a Ie33 Philips Ultrasound system according to European and American guidelines. (135, 151) Standard parasternal and apical views were used and digital loops of 3 cardiac cycles with associated electrocardiogram information were stored on to the hard disk of the machine. The methodology used for image acquisition and measurements is described in detail in Chapter 2. Offline analysis was performed according to American and European echocardiography guidelines. (135, 151) On a subgroup of patients, speckle tracking analysis was performed to obtain global longitudinal and circumferential strain (GLS/GCS). Parasternal short axis views and apical 2, 3 and 4 chamber views were analysed using the 2D Cardiac Performance Analysis, TomTec Imaging System, Munich, Germany. The methodology used is described in detail in Chapter 2.

Information on pregnancy outcomes were obtained from the Hospital's perinatal database. Development of GDM and hypertensive disorders of pregnancy were defined as previously described (Chapter 2). Birth weight (BW) percentiles were calculated, as previously described (Chapter 2).

Statistical analyses

The statistical analysis is described in further detail in Chapter 2. In brief, the groups were compared at each time point (trimester) and within each group the time points were compared using the unpaired Student t-test/Mann-Whitney or chi-square ($\chi 2$) for numerical and categorical data respectively. Differences were considered statistically significant at $p<0.05$.

Hierarchical modelling was used for further analysis of haemodynamic, geometric, diastolic and strain imaging variables using multilevel linear mixed-effects models. The fixed effect component included time (the 3 visits), study group, age, race, GDM, smoking, gestation and first-order interaction between time and study group. The correlation of CO, total peripheral resistance (TPR) and mean arterial pressure (MAP) with BW were assessed by Pearson's correlation. All analyses were performed using IBM SPSS Statistics, version 26.0, 2019 (*IBM Corp., Armonk, New York, USA*).

Sample size calculation was performed using the G*Power software (G*Power for Windows Os X, v. 3.1, February 2020, Heinrich-Heine-Universität, Dusseldorf, Germany).(152) There are no previous studies investigating the cardiovascular system pregnant women with previous bariatric surgery. Therefore, it was difficult to be accurate on the number of subjects required in each group to obtain results with adequate power. Using studies of individuals before and after bariatric surgery outside of the context of pregnancy we have estimated sample sizes. To demonstrate a similar effect to Owan et al.(102) in CO and Kaier et al.(108) for LV mass, mitral inflow E-wave/A-wave (E/A) ratio and GLS for an alpha = 0.05 and a power of 80%, we would have needed 33 study subjects in each group and each trimester.

Results

The study included, 33 pregnant women after bariatric surgery and 33 women without surgery matched for pre-surgery BMI, age, race and diabetes status. The maternal characteristics of the study population are given in Table 3.1. Sixteen women in the post-bariatric group had undergone a gastric bypass, 12 had undergone a sleeve gastrectomy and 5 had undergone a gastric band. The mean time from surgery to conception was 48.7 months. As expected, there were no significant differences in the maternal demographics between the study groups except BMI at booking. None of the women in the post-bariatric group developed hypertensive disorders and these women, overall, delivered smaller babies than the women without surgery.

Table 3.1 Maternal demographic characteristics and pregnancy outcomes of the study participants.

Variable	**No-surgery N=33**	**Post-bariatric surgery N=33**	**P value**
Age (years)	32.9 (5.3)	33.2 (5.9)	0.88
Racial group			
White, n (%)	27 (81.8)	28 (84.8)	0.74
Other, n (%)	6 (18.2)	5 (15.2)	
BMI at booking (kg/m2)	41.3 (6.6)	33.3 (7.0)	<0.01
BMI pre-surgery (kg/m2)	-	44.4 (6.3)	0.06*
1st Trimester weight (kg)	113.6 (93.2-131.7)	89.6 (77.125-106.6)	<0.001
2nd Trimester weight (kg)	114.4 (96.55-133.8)	93.3 (79.9-108.8)	<0.001
3rd Trimester (kg)	116.7 (102.7-136.6)	95 (80.1-112.1)	<0.001
Weight change T2-T1	1.8 (-0.15-3.95)	3.8 (1.3-4.8)	0.08
Weight change T3-T2	2.8 (2-4.25)	2.8 (1.3-4.8)	0.70
Weight change T3-T1	4.9 (1.7-7.5)	6.1 (1.6-9.6)	0.40
Parity			
Nulliparous, n (%)	14 (42.4)	21 (63.6)	0.08
Parous, n (%)	19 (57.6)	12 (36.4)	
Conception			
Spontaneous, n (%)	30 (90.2)	31 (95.1)	0.64
Assisted, n (%)	4 (9.8)	2 (4.9)	
Smoking			
No, n (%)	31 (95.1)	30 (90.2)	0.64
Yes, n (%)	2 (4.9)	4 (9.8)	
Hypertensive disorders of pregnancy			
No, n (%)	29 (87.9)	33 (100)	<0.001
Yes, n (%)	4 (12.1)	0 (0)	
Gestational diabetes mellitus			

No, n (%)	25 (75.8)	26 (78.8)	0.77
Yes, n (%)	8 (24.2)	7 (21.2)	
Mode of delivery			
Spontaneous vaginal delivery, n (%)	14 (42.4)	16 (48.5)	0.16
Operative vaginal delivery, n (%)	3 (0.1)	3 (0.1)	1
Caesarean section, n (%)	16 (48.5)	14 (42.4)	0.16
Gestational age at delivery (wks)	39.1 (38.2-39.9)	38.8 (37.5-39.6)	0.54
Birth weight (g)	3505 (3070-3844)	3230 (2480-3420)	0.01
Birthweight percentiles (%)	74.1 (34.7-92.5)	30.8 (9.6-50.6)	<0.01

Data are expressed as mean (standard deviation), median (interquartile range) or n (%). *T1*, first trimester; *T2,* second trimester; *T3,* third trimester

*comparison between BMI in early pregnancy in the no-surgery group and BMI pre-surgery in the post-bariatric group

Hemodynamic variables

The median raw values of the haemodynamic variables in the three trimesters of pregnancy and comparisons between the groups are given in Table 3.2. Within each group the trimesters were compared and for significant differences, the mean difference and p values for trimester 1 vs 2, trimester 1 vs 3 and trimester 2 vs 3 are given in Table 3.3.

Table 3.2. Haemodynamic variables, median (interquartile range) for each trimester and group with p values of group comparison

	1st Trimester 11-14 weeks			**2nd Trimester 20-24 weeks**			**3rd Trimester 30-32 weeks**		
	No-surgery N=20	**Post-bariatric surgery N=20**	**P**	**No-surgery N=33**	**Post-bariatric surgery N=33**	**P**	**No-surgery N=30**	**Post-bariatric surgery N=30**	**P**
SBP (mmHg)	113.8 (107.3-130)	101.5 (93.3-106.8)	**<0.001**	112 (100.5-116.5)	99 (91-109)	**<0.01**	111 (103.5-121.5)	103.5 (93-110)	**<0.01**
DBP (mmHg)	62.8 (60-79)	61 (59.3-66.3)	0.15	65 (61-70.5)	59 (55.5-62.3)	**<0.001**	65 (60.5-71)	62 (57.5-66.5)	**<0.05**
MAP (mmHg)	81.4 (75.6-94.9)	75 (69.5-79.5)	**<0.01**	80.3 (75.8-86.7)	74.3 (67.2-78.3)	**<0.001**	80.1 (75.6-86.4)	76.7 (70.3-80.7)	**0.02**
HR (bpm)	83 (75.3-88.8)	73 (65.5-75)	**<0.01**	84 (74.5-93)	75 (69-85.5)	**0.01**	93.5 (83.8-98)	80 (70-87)	**<0.001**
LVOT VTI (mm)	23.7 (20.9-28.2)	22 (20.7-25)	0.28	25.8 (22.9-28.8)	22.6 (21-26.6)	**0.03**	25.7 (20.7-27.6)	22.9 (21-24.7)	0.17
SV (ml)	80.9 (72.5-92.2)	72 (66.6-79.6)	0.07	86.5 (72.2-104.6)	79.6 (72-87.3)	0.07	85.7 (77.3-99.7)	80.5 (73-87.9)	0.08
CO (L/min)	6.9 (6.3-7.4)	5 (4.5-5.6)	**<0.001**	7.5 (6.4-8.5)	5.9 (5.3-6.9)	**<0.001**	7.7 (6.3-9.2)	6.2 (5.7-7.0)	**<0.01**
TPR (dynes/s per cm^5)	1002.9 (871.6-1158.9)	1178.5 (990.6-1349.6)	**<0.05**	874.7 (752-976.6)	992.6 (856.7-1094.8)	0.06	835.4 (675.6-986.4)	971.5 (868.6-1083.9)	**<0.01**
SVI (mm/BSA)	39.5 (30.8-43.8)	36.6 (32.4-39.9)	0.48	40 (36-48.3)	39.5 (37.2-44.7)	0.77	39.9 (35.4-45.6)	40.5 (35-47.6)	0.92
CI (mm/BSA)	3.2 (2.9-3.5)	2.5 (2.3-2.9)	**<0.01**	3.4 (2.9-3.8)	3 (2.7-3.4)	**0.01**	3.6 (3-4.3)	3.2 (2.8-3.6)	**0.01**

BSA, body surface area*; CO*, cardiac output; *CI* cardiac index; *DBP*, diastolic blood pressure; *HR*, heart rate; *LVOT TVI*, left ventricle outflow tract velocity time integral; *MAP*, mean arterial pressure; *SV*, stroke volume; *SVI*, stroke volume index; *SBP*, systolic blood pressure; *TPR*, total peripheral resistance

Table 3.3. Mean difference of haemodynamic variables between trimesters in the two groups of women (actual values given in Table 3.2). All comparisons have been adjusted by the Bonferroni correction for multiple tests. (T1: 11-14 weeks, T2: 20-24 weeks, T3: 30-32 weeks)

No-surgery, N=18						
	T 1 vs 2		T 1 vs 3		T 2 vs 3	
	Mean difference	P	Mean difference	P	Mean difference	P
HR (bpm)	0.8 (11.2)	0.76	7.2 (11.0)	0.04	6.4 (12.2)	0.14
CO (L/min)	0.3 (1.1)	0.46	1.1 (1.8)	0.02	0.8 (1.8)	0.38
TPR (dynes/s per cm5)	-49.6 (168.5)	0.46	-90.2 (232.3)	0.03	-70.2 (200.3)	0.53
CI (mm/BSA)	0.1 (0.5)	0.66	0.5 (0.8)	0.36	0.4 (0.7)	0.33
Post-bariatric surgery, N=18						
	T 1 vs 2		T 1 vs 3		T 2 vs 3	
	Mean difference	P	Mean difference	P	Mean difference	P
HR (bpm)	3 (6.6)	0.56	2 (22.5)	0.03	1 (22.0)	0.28
CO (L/min)	0.8 (1.2)	0.09	1.2 (1.5)	0.02	0.4 (0.9)	0.18
TPR (dynes/s per cm5)	-144.4 (157.5)	0.07	-150.3 (253.8)	0.02	-30.4 (101.3)	0.61
CI (mm/BSA)	0.4 (0.6)	0.09	0.6 (0.8)	0.01	0.2 (0.7)	0.13

BSA, body surface area*; CO*, cardiac output; *CI* cardiac index; *HR*, heart rate; *TPR*, total peripheral resistance

Mixed model analysis was used to compare the haemodynamic variables between groups at each trimester and overall, after adjustment for age, race, gestational age, GDM and smoking. The overall group comparison across all trimesters is given in Table 3.4 and the estimated marginal means at each trimester for each group is given in Table 3.5.

Table 3.4. Multilevel linear mixed-effects models for Log10 haemodynamic variables, overall group comparison across all trimesters

Overall group comparisons (All trimesters)		
	Mean Difference No-surgery – Post-bariatric surgery	**P**
Log10 SBP (mmHg)	0.047 (0.033-0.061)	**<0.001**
Log10 DBP (mmHg)	0.04 (0.024-0.057)	**<0.001**
Log 10 MAP (mmHg)	0.043 (0.029-0.057)	**<0.001**
Log10 HR (bpm)	0.05 (0.032-0.068)	**<0.001**
Log10 SV (ml)	0.042 (0.015-0.068)	**<0.01**
Log10 CO (L/min)	0.093 (0.065-0.12)	**<0.001**
Log10 TPR (dynes/s per cm^5)	-0.051 (-0.079-(-0.022))	**<0.01**
Log10 SVI (mm/BSA)	0.009 (-0.016-0.035)	0.46
Log10 CI (mm/BSA)	0.061 (0.036-0.085)	**<0.001**

BSA, body surface area*; CO*, cardiac output; *CI* cardiac index; *DBP*, diastolic blood pressure; *HR*, heart rate; *MAP*, mean arterial pressure; *SV*, stroke volume; *SVI*, stroke volume index; *SBP*, systolic blood pressure; *TPR*, total peripheral resistance

Table 3.5. Multilevel linear mixed-effects models for Log10 hemodynamic variables. Estimated marginal means (95% CI) for each trimester and group are given.

	1st Trimester			**2nd Trimester**			**3rd Trimester**		
	No-surgery N=20	**Post-bariatric surgery N=20**	**P**	**No-surgery N=33**	**Post-bariatric surgery N=33**	**P**	**No-surgery N=30**	**Post-bariatric surgery N=30**	**P**
Log10 SBP (mmHg)	2.06 (2.04 -2.11)	2.02 (1.99 -2.05)	**<0.001**	2.08 (2.03 -2.08)	2.02 (1.99 -2.04)	**<0.01**	2.09 (2.04 -2.09)	2.04 (2 -2.05)	**<0.001**
Log10 DBP (mmHg)	1.83 (1.8 -1.87)	1.8 (1.76 -1.83)	**0.02**	1.83 (1.8 -1.85)	1.77 (1.75 -1.8)	**<0.001**	1.83 (1.81 -1.86)	1.8 (1.78 -1.83)	**0.04**
Log 10 MAP (mmHg)	1.93 (1.9 -1.96)	1.88 (1.86 -1.91)	**<0.01**	1.93 (1.9 -1.94)	1.87 (1.85 -1.89)	**<0.001**	1.95 (1.9 -1.97)	1.89 (1.87 -1.92)	**0.01**
Log10 HR (bpm)	1.95 (1.92 -1.99)	1.9 (1.86 -1.93)	**<0.01**	1.96 (1.93 -1.99)	1.92 (1.88 -1.95)	**<0.01**	1.99 (1.96 -2.02)	1.94 (1.9 -1.97)	**<0.01**
Log10 SV (ml)	1.9 (1.85 -1.95)	1.86 (1.81 -1.91)	**0.04**	1.94 (1.88 -1.98)	1.9 (1.85 -1.94)	0.07	1.94 (1.89 -1.98)	1.92 (1.89 -1.95)	0.13
Log10 CO (L/min)	3.85 (3.8 -3.9)	3.75 (3.7 -3.81)	**<0.001**	3.9 (3.85 -3.94)	3.81 (3.76 -3.86)	**<0.01**	3.93 (3.88 -3.98)	3.83 (3.78 -3.88)	**<0.001**
Log10 TPR (dynes/s per cm^5)	2.99 (2.93 -3.04)	3.04 (2.98 -3.09)	**0.04**	2.93 (2.88 -2.98)	2.96 (2.91 -3.01)	0.15	2.9 (2.85 -2.95)	2.95 (2.91 -3.02)	**0.01**
Log10 SVI (mm/BSA)	1.55 (1.5 -1.6)	1.53 (1.48 -1.58)	0.37	1.58 (1.54 -1.63)	1.57 (1.53 -1.62)	0.69	1.58 (1.53 -1.62)	1.57 (1.53 -1.62)	0.93
Log10 CI (mm/BSA)	3.5 (3.45 -3.55)	3.43 (3.38 -3.48)	**<0.01**	3.54 (3.5 -3.58)	3.49 (3.45 -3.53)	**0.02**	3.57 (3.53 -3.62)	3.51 (3.46 -3.55)	**0.01**

BSA, body surface area*; CO*, cardiac output; *CI* cardiac index; *DBP*, diastolic blood pressure; *HR*, heart rate; *MAP*, mean arterial pressure; *SV*, stroke volume; *SVI*, stroke volume index; *SBP*, systolic blood pressure; *TPR*, total peripheral resistance

Within each group there was no significant difference in blood pressure across the trimesters. Between groups, the post-bariatric group had a lower systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP) in all trimesters and in the overall analysis compared to the no-surgery group (Table 3.4, Figure 3.1).

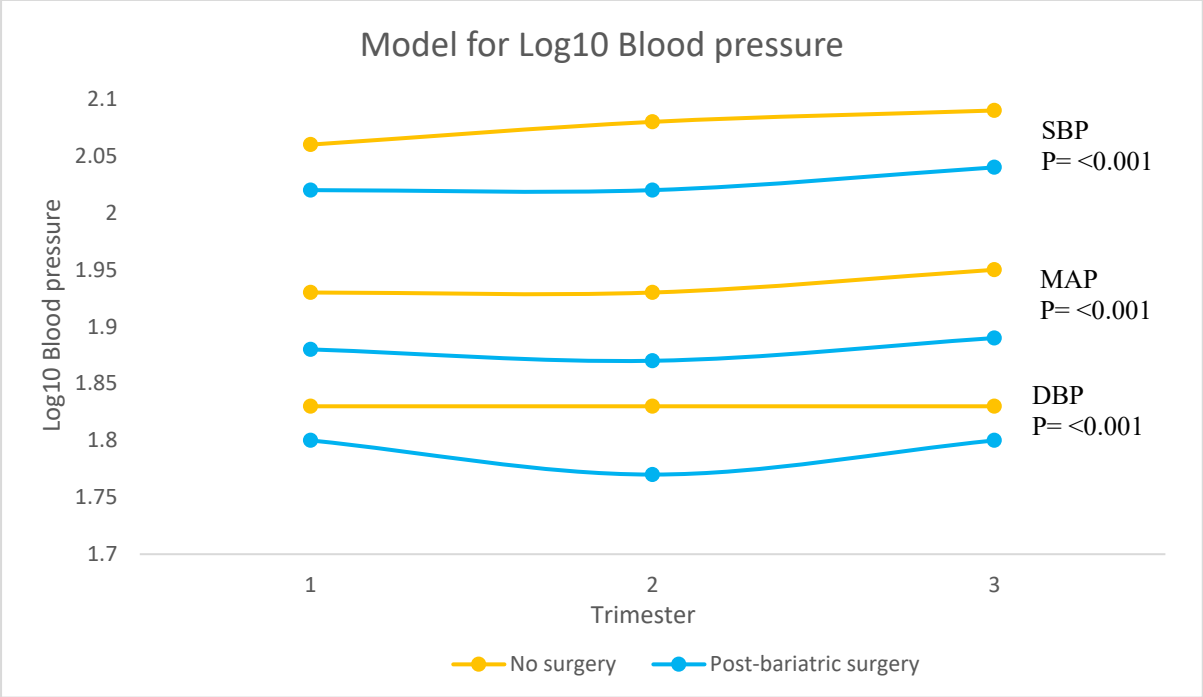


Figure 3.1. Mixed model analysis systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP) across trimesters in both groups.

The HR was significantly higher in the third compared to first trimester in both groups. When comparing the groups, the HR was lower in all trimesters in the post-bariatric women compared to the no-surgery group and in the overall analysis across all trimesters (Table 3.4, Figure 3.2).

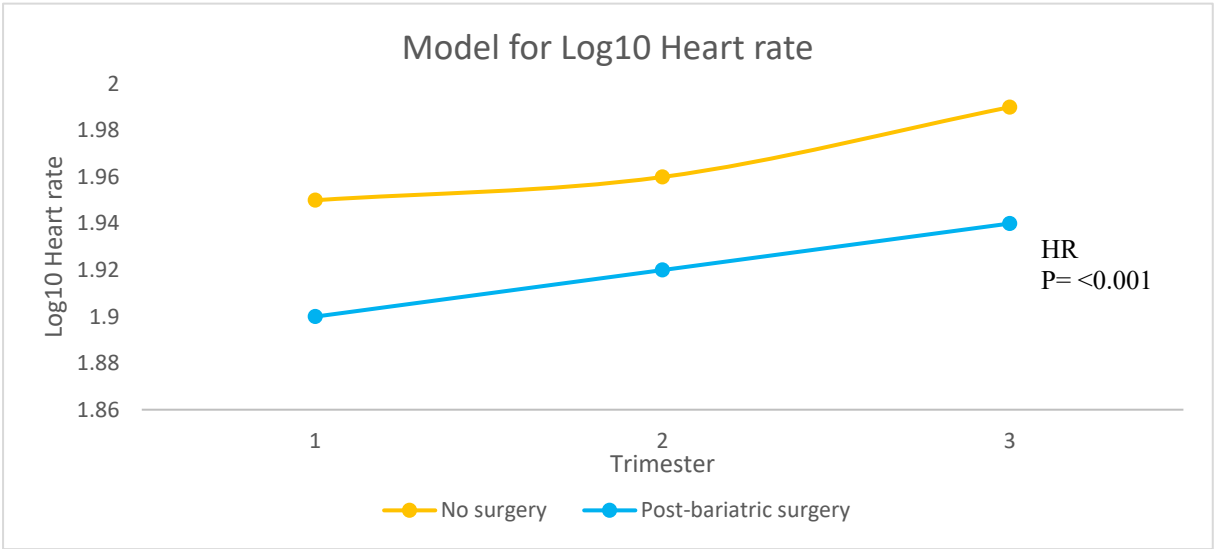


Figure 3.2. Mixed model analysis for heart rate across trimesters in both groups

The SV and CO trended up in both groups with a significant increase in CO from the first to the third trimester. Between the second and third trimester there was a plateau in SV in the no-surgery group and a small non-significant increase in the post-bariatric group. When comparing the groups, the overall analysis across all trimesters found that the SV and CO were significantly lower in the post-bariatric group compared to the no-surgery group (Table 3.4, Figure 3.3) At each trimester the CO was lower in the post-bariatric group compared to the no-surgery group, the SV was lower in the post-bariatric group in the first trimester.

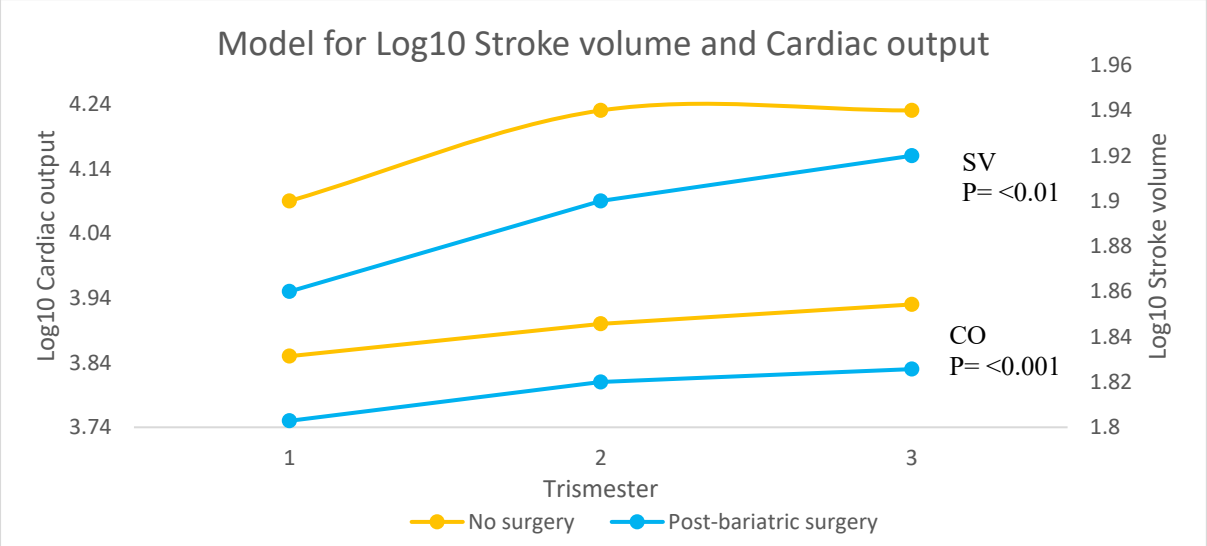


Figure 3.3. Mixed model analysis for stroke volume (SV) and cardiac output (CO across trimesters in both groups

The TPR trended down across trimesters in both groups and was significantly lower in the third compared to first trimester. When comparing the groups, the TPR was higher in the post-bariatric compared to the no-surgery group in the overall analysis (Table 3.4, Figure 3.4).

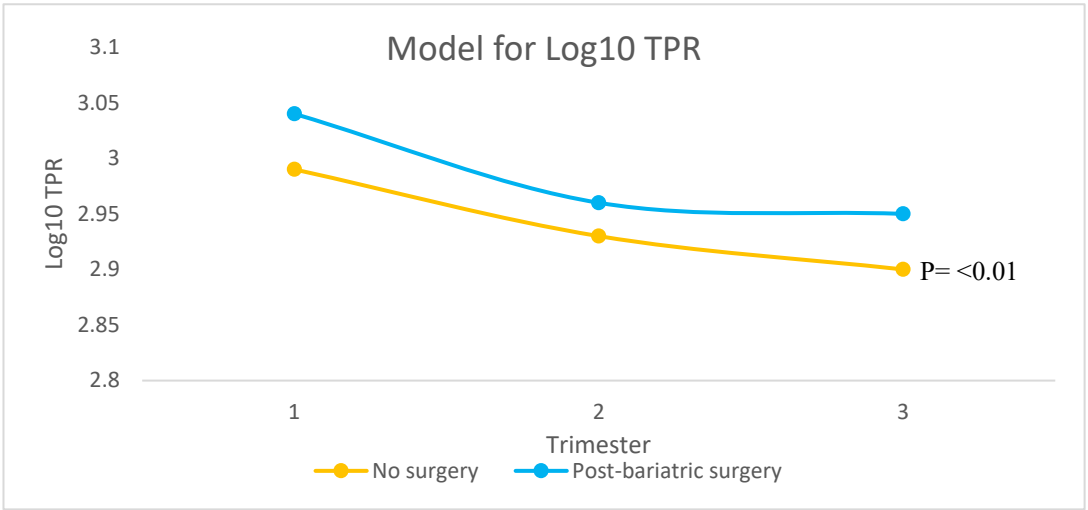


Figure 3.4 Mixed model analysis for Log10 total peripheral resistance (TPR) in both groups examined.

Cardiac geometry

The mean raw values of the cardiac geometry in the three trimesters of pregnancy and comparisons between the groups are given in Table 3.6. Within each group the trimesters were compared and for significant differences, the mean difference and p values for trimester 1 vs 2, trimester 1 vs 3 and trimester 2 vs 3 are given in Table 3.7.

Table 3.6. Cardiac geometry, mean (standard deviation) for each trimester and group with p values of group comparison

	1st Trimester 11-14 weeks			**2nd Trimester 20-24 weeks**			**3rd Trimester 30-32 weeks**		
	No-surgery N=20	**Post-bariatric surgery N=20**	**P**	**No-surgery N=33**	**Post-bariatric surgery N=33**	**P**	**No-surgery N=30**	**Post-bariatric surgery N=30**	**P**
LA (mm)	40.3 (4.6)	38.2 (4.1)	0.10	40.4 (5.2)	40.2 (3.7)	0.84	40.3 (4.6)	39.3 (4.9)	0.39
LA index (mm/BSA)	18.7 (2.3)	19.3 (2.1)	0.4	19.8 (2.6)	20.4 (2.5)	0.17	18.7 (2.1)	19.9 (3.3)	0.08
Aorta (mm)	27.3 (3)	26.1 (2.5)	0.16	27.7 (3.1)	27.2 (2.1)	0.44	27.7 (3.2)	27.4 (2.2)	0.73
Ascending aorta (mm)	27.9 (3.1)	28.3 (1.5)	0.62	27.9 (2.5)	27.5 (2.7)	0.56	27.8 (2.7)	27.6 (2.5)	0.80
LVOT (mm)	20.8 (1.6)	20.4 (1.1)	0.30	21.1 (1.8)	20.9 (1.3)	0.59	21.5 (1.7)	21.1 (1.3)	0.37
IVS (mm)	8.9 (1.6)	8.2 (1.3)	0.08	9.2 (1.3)	8.5 (1.3)	**0.02**	9.2 (1.3)	8.5 (1.2)	**0.03**
LVEDD (mm)	48.2 (6)	48.9 (3.7)	0.64	49.9 (5.2)	49.6 (4.3)	0.78	51.2 (5.5)	50.7 (4.2)	0.68
LVEDD index (mm/BSA)	22.5 (2.8)	23.6 (6)	0.38	23.2 (2.7)	25.1 (3)	0.05	24.1 (2.7)	25.6 (2.8)	0.05
PW (mm)	9.7 (1.5)	8.7 (0.9)	**0.01**	9.6 (1.5)	8.8 (1)	**0.01**	10.2 (1.4)	9 (1.1)	**<0.001**
RWT	0.39 (0.09)	0.36 (0.05)	**0.03**	0.39 (0.07)	0.36 (0.05)	**0.04**	0.41 (0.07)	0.37 (0.05)	**0.01**
LVM (g)	161.1 (34.5)	144.3 (24)	**0.03**	173.5 (36.4)	153.2 (32.1)	**0.02**	187.4 (40.2)	162.5 (36.5)	**0.01**
LVM index (g/BSA)	74.2 (14.3)	72.6 (9.5)	0.66	80 (15.3)	77.1 (14.4)	0.43	87 (17.1)	78.9 (20.6)	0.09

BSA, body surface area*; IVS*, interventricular septum; *LA*, left atrium diameter; *LVEDD*, left ventricle end-diastolic diameter; *LVM*, left ventricular mass; *LVOT*, left ventricle outflow tract; *PW*, posterior wall thickness; *RWT*, relative wall thickness

Table 3.7. Mean difference in LV mass and LV mass index between trimesters in the two groups of women (actual values given in Table 3.6). All comparisons have been adjusted by the Bonferroni correction for multiple tests. (T1: 11-14 weeks, T2: 20-24 weeks, T3: 30-32 weeks)

No-surgery, N=18						
	T 1 vs 2		T 1 vs 3		T 2 vs 3	
	Mean difference	P	Mean difference	P	Mean difference	P
LVM (g)	10.7 (29.2)	**0.02**	17.2 (34.1)	**0.04**	8.1 (26.3)	0.68
LVM index (g/BSA)	5.0 (12.8)	**0.01**	9.3 (21.7)	**0.02**	4.4 (24.5)	0.53
Post-bariatric surgery, N=18						
	T 1 vs 2		T 1 vs 3		T 2 vs 3	
	Mean difference	P	Mean difference	P	Mean difference	P
LVM (g)	9.6 (30.5)	0.16	19.1 (21.0)	**<0.05**	11.1 (31.0)	0.32
LVM index (g/BAS)	3.1 (9.0)	0.1	14.1 (19.1)	**0.02**	4.2 (15.2)	0.24

BSA, body surface area; *LVM*, left ventricular mass

Mixed model analysis was used to compare the cardiac geometry between groups at each trimester and overall, after adjustment for age, race, gestational age, diabetes status and smoking. The overall group comparison across all trimesters is given in Table 3.8 and the estimated marginal means at each trimester for each group is given in Table 3.9.

Table 3.8. Multilevel linear mixed-effects models for cardiac geometry, overall group comparison across all trimesters

Overall group comparisons (All trimesters)		
	Mean Difference No-surgery – Post-bariatric surgery (95% Confidence Interval for Difference)	**P**
LA (mm)	0.606 (-1.368-2.581)	0.55
LA index (mm/BSA)	0.837 (-1.603-(-0.072))	0.08
IVS (mm)	0.7 (0.304-1.096)	**<0.01**
LVEDD (mm)	0.291 (-1.792-1.209)	0.7
LVEDD index (mm/BSA)	1.476 (-2.617-(-0.335))	0.05
PW (mm)	0.939 (0.545-1.333)	**<0.001**
RWT	0.044 (0.023-0.065)	**<0.001**
LVM (g)	16.976 (6.22-27.732)	**<0.01**
LVM index (g/BSA)	3.581 (-1.214-8.375)	0.14

BSA, body surface area*; IVS*, interventricular septum; *LA*, left atrium diameter; *LVEDD*, left ventricle end-diastolic diameter; *LVM*, left ventricular mass; *PW*, posterior wall thickness; *RWT*, relative wall thickness

Table 3.9. Multilevel linear mixed-effects models for cardiac geometry, estimated marginal means (95% CI) for each trimester and group are given.

	1st Trimester			**2nd Trimester**			**3rd Trimester**		
	No-surgery N=20	**Post-bariatric surgery N=20**	**P**	**No-surgery N=33**	**Post-bariatric surgery N=33**	**P**	**No-surgery N=30**	**Post-bariatric surgery N=30**	**P**
LA (mm)	39 (37.2 -42.8)	37.6 (34.8 -40.4)	0.12	39.5 (37.5 -42.4)	38.7 (37.2 -42.2)	0.85	40 (37.5 -42.4)	38.9 (36.1 -41.3)	0.28
LA index (mm/BSA)	17.7 (16.3 -19.2)	17.8 (16.4 -19.3)	0.84	17.6 (16.3 -18.9)	18 (17.7 -20.4)	0.09	18.9 (16.2 -18.9)	18.5 (17.1 -19.9)	0.19
IVS (mm)	9.7 (8.9 -10.4)	8.9 (8.2 -9.7)	**<0.05**	10 (9.4 -10.7)	9.3 (8.6 -10)	**0.02**	9.9 (9.3 -10.6)	9.3 (8.6 -10)	**0.03**
LVEDD (mm)	47.9 (44.1 -49.7)	48.3 (45.4 -51.2)	0.31	49.2 (46.6 -51.7)	48.9 (46.3 -51.6)	0.80	50.4 (47.7 -53)	50.1 (47.3 -52.9)	0.86
LVEDD index (mm/BSA)	20.5 (18.2 -22.8)	21.7 (19.4 -24)	0.12	21.3 (19.8 -22.9)	23.2 (21.6 -24.8)	**0.06**	22.3 (20.8 -23.9)	23.7 (22 -25.3)	0.08
PW (mm)	9.8 (9.1 -10.5)	8.9 (8.2 -9.6)	**<0.05**	9.9 (9.3 -10.6)	9 (8.3 -9.7)	**<0.01**	10.3 (9.7 -10.9)	9.4 (8.7 -10)	**<0.01**
RWT	0.40 (0.38-0.46)	0.36 (0.33-0.41)	**0.03**	0.41 (0.37-0.44)	0.36 (0.33-0.40)	**0.02**	0.41 (0.38-0.45)	0.37 (0.33-0.41)	**0.01**
LVM (g)	165 (145.9 - 184.2)	154.8 (135.1 - 174.6)	**0.03**	183.1 (164.5 - 201.7)	164 (144.6 -183.3)	**0.02**	195.2 (175.5 - 214.9)	173.6 (152.9 - 194.3)	**0.04**
LVM index (g/BAS)	72.5 (64.2 -80.8)	72.2 (63.6 -80.8)	0.84	80.3 (72.2 -88.4)	77.3 (68.9 -85.7)	0.29	86.6 (77.6 -95.7)	79.2 (69.9 -88.5)	0.11

BSA, body surface area*; IVS*, interventricular septum; *LA*, left atrium diameter; *LVEDD*, left ventricle end-diastolic diameter; *LVM*, left ventricular mass; *PW*, posterior wall thickness; *RWT*, relative wall thickness

For both groups, the LA (left atrial) diameter, left ventricle end-diastolic diameter (LVEDD), interventricular septum (IVS) diameter, posterior wall (PW) diameter and relative wall thickness (RWT) all trended upwards across trimesters however there was no significant differences, whereas LV mass significantly increased during gestation in both groups. When comparing the groups, overall across all trimesters, the IVS, PW diameter, LV mass and RWT were significantly lower in the post-bariatric compared to the no-surgery group (Table 3.8, Figures 3.5- 3.8).

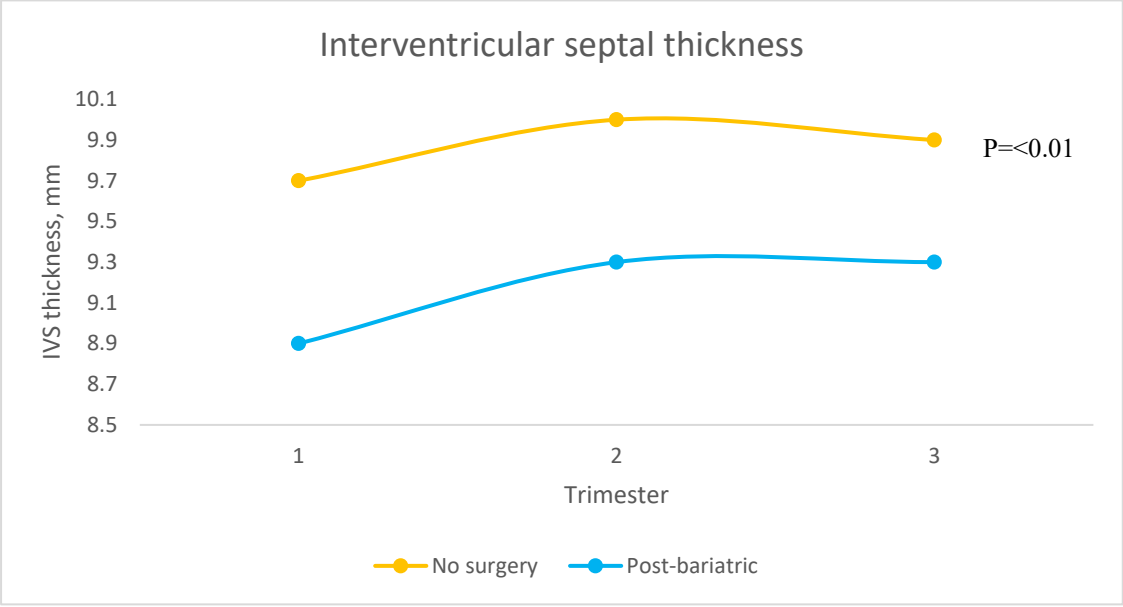


Figure 3.5. Mixed model analysis for interventricular septal thickness in both groups examined

.

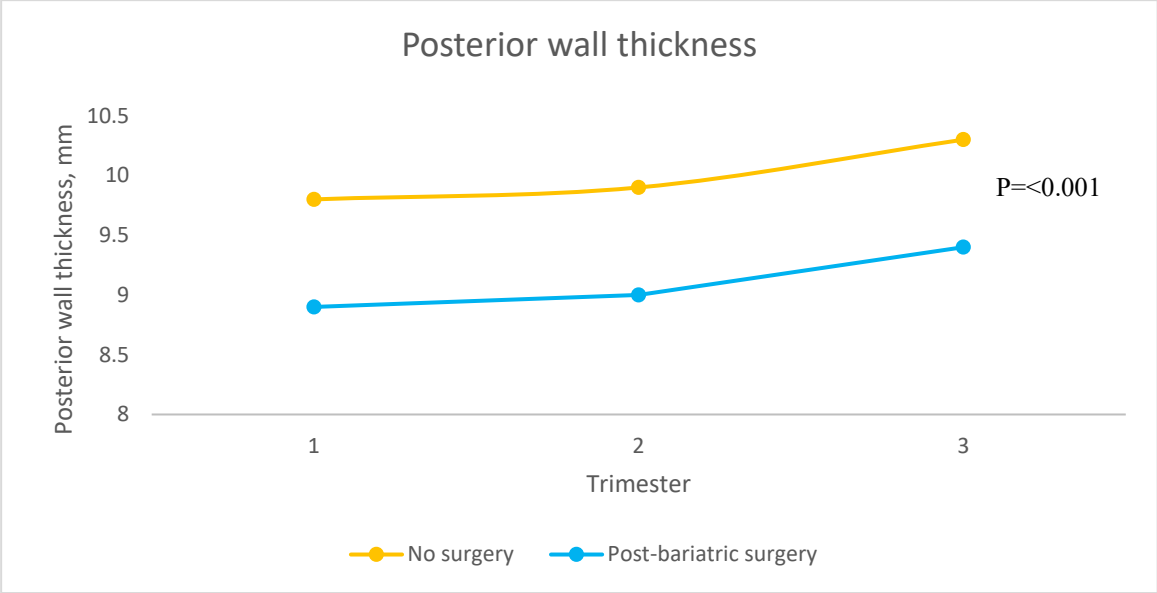


Figure 3.6. Mixed model analysis for posterior wall thickness in both groups examined.

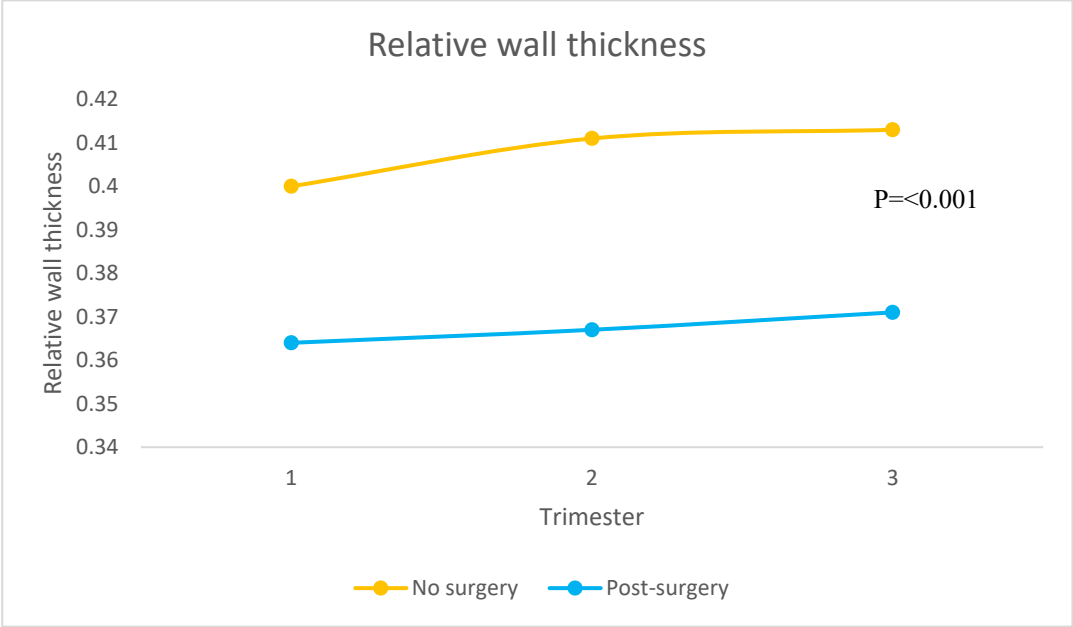


Figure 3.7. Mixed model analysis for relative wall thickness (2 x left ventricle posterior wall diameter)/ left ventricle end diastolic diameter) in both groups examined.

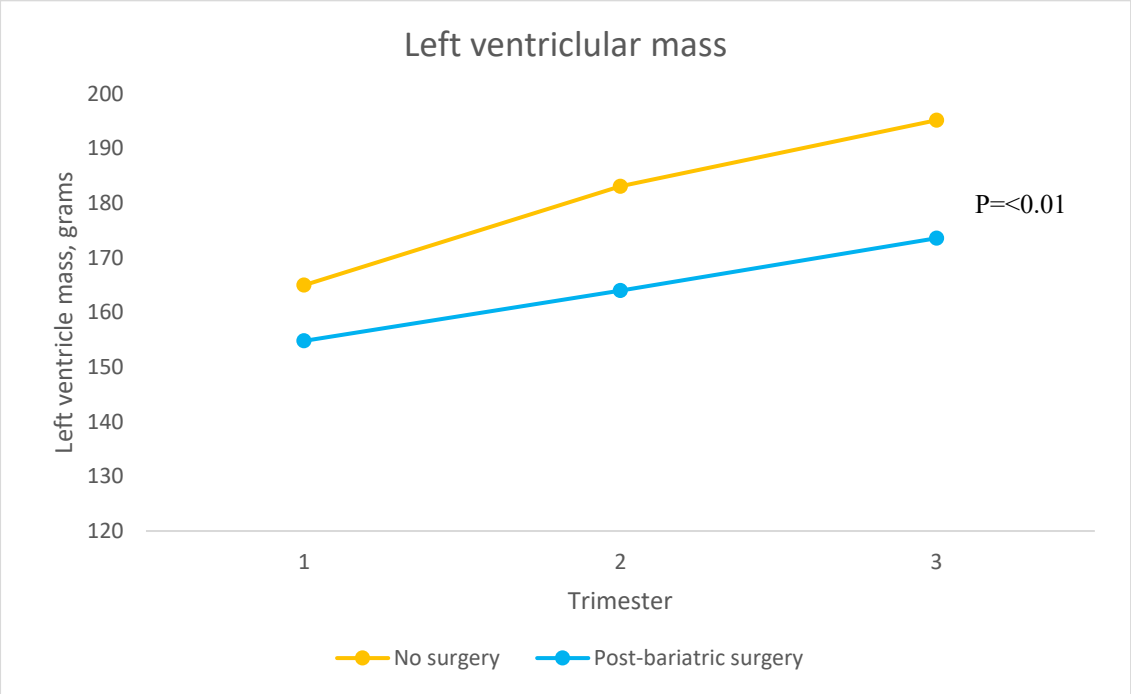


Figure 3.8. Mixed model analysis for left ventricular mass across trimesters in both groups examined.

Systolic, diastolic and longitudinal function

The mean raw values of the systolic, diastolic and longitudinal function in each trimester and comparisons between the groups are given in Table 3.10. Within each group the trimesters were compared and for significant differences, the mean difference and p values for trimester 1 vs 2, trimester 1 vs 3 and trimester 2 vs 3 are given in Table 3.11.

Table 3.10. Systolic, diastolic and longitudinal function, mean (standard deviation) for each time point and group with p values.

	1st Trimester 11-14 weeks			**2nd Trimester 20-24 weeks**			**3rd Trimester 30-32 weeks**		
	No-surgery N=20	**Post-bariatric surgery N=20**	**P**	**No-surgery N=33**	**Post-bariatric surgery N=33**	**P**	**No-surgery N=30**	**Post-bariatric surgery N=30**	**P**
Systolic function									
EDV (mm)	101 (20.5)	93.5 (14.9)	0.16	101.4 (19.2)	95.9 (15.9)	0.21	106.2 (21.6)	97.2 (14.5)	0.06
EDV index (mm/BSA)	46.5 (7.1)	47.3 (8.4)	0.69	46.9 (8)	48.5 (8.3)	0.43	48.9 (8.1)	48.9 (6.8)	0.99
ESV (mm)	41 (11.1)	35.3 (6.6)	**0.04**	41.2 (11.3)	37.5 (7.8)	0.13	44.3 (11.4)	39.1 (8.3)	**<0.05**
ESV index (mm/BSA)	18.8 (4)	17.9 (4.1)	0.45	19 (4.6)	18.9 (3.9)	0.96	20.4 (4.5)	19.6 (3.7)	0.47
EF (%)	59.9 (4.4)	61.9 (5.4)	0.16	59.5 (5.2)	61.3 (4.9)	0.14	59.9 (4.8)	60.1 (5.3)	0.88
TDI s' (cm)	12.6 (2.5)	12.8 (2.6)	0.79	13.1 (2.4)	13.4 (2.5)	0.64	13.1 (2.9)	12.4 (2.2)	0.33
Diastolic function									
E velocity (m/s)	81.2 (14.4)	84.7 (7.9)	0.34	83.5 (18)	86.2 (16.9)	0.54	78.4 (21)	77 (15.7)	0.76
A velocity (m/s)	62 (11.1)	53.3 (9.9)	**0.01**	64 (13.1)	54.7 (10.9)	**<0.001**	67.4 (14.6)	54.6 (9.8)	**<0.001**
E/A ratio	1.3 (0.3)	1.6 (0.3)	**<0.001**	1.3 (0.3)	1.6 (0.3)	**<0.001**	1.2 (0.3)	1.4* (0.3)	**<0.001**
E' lateral (m/s)	14.3 (2.8)	16.3 (3.5)	**0.03**	13.2 (2.8)	15.3 (3.4)	**0.01**	12.4 (2.8)	13.1 (3)	0.34
E' medial (m/s)	9.9 (2.3)	11.3 (2.3)	**<0.05**	9.8 (2.4)	11 (2.2)	**<0.05**	8.9 (1.9)	9.9 (2.6)	0.11

E/ E' ratio	6.9 (1.4)	6.1 (1.9)	0.06	7.4 (1.8)	6.8 (1.4)	0.11	7.6 (2.6)	6.9 (1.9)	0.25
LAV (ml)	61.3 (14.3)	55.5 (7.4)	0.10	66 (12.9)	59.3 (9)	**0.03**	67.4 (11.8)	60.5 (7.8)	**0.01**
LAV index (ml/BSA)	28.3 (5.8)	28 (3.7)	0.89	30.3 (5.7)	30.1 (4.8)	0.85	31.3 (5.5)	30.7 (5.2)	0.69
Longitudinal function									
TAPSE (mm)	22.3 (3.2)	22 (3.4)	0.73	23.1 (4.3)	23.2 (3.1)	0.93	21 (3.5)	21.2 (4.1)	0.86
MAPSE septal (mm)	15 (2.4)	14.7 (2.7)	0.73	14 (1.9)	14.4 (2.5)	0.45	12.7 (2)	13.5 (2.9)	0.21
MAPSE lateral (mm)	17 (3.2)	16.5 (2.5)	0.56	16.3 (3.2)	16.5 (2.4)	0.87	13.8 (2.7)	15.1 (2.3)	0.06

BSA, body surface area*; E/A ratio*, mitral inflow E-wave/A-wave filling; *E' lateral*, tissue Doppler imaging E prime measured at lateral mitral annulus; *E' medial*, tissue Doppler imaging E prime measured at medial mitral annulus; *E/E' ratio*, E-wave mitral inflow/ mean E' lateral and E' medial; *EF*, ejection fraction; *EDV*, end-diastolic volume; *ESV*, end-systolic volume; *LAV*, left atrial volume; *TDI s'*, tissue Doppler imaging s' at the lateral tricuspid annulus; *MAPSE*, mitral annular plane systolic excursion; TAPSE, tricuspid annular plane systolic excursion

Table 3.11. Mean difference in E/A ratio, LA volume and LA volume index between trimesters in the two groups of women (actual values given in Table 3.10). All comparisons have been adjusted by the Bonferroni correction for multiple tests. (T1: 11-14 weeks, T2: 20-24 weeks, T3: 30-32 weeks)

No-surgery, N=18						
	T 1 vs 2		T 1 vs 3		T 2 vs 3	
	Mean difference	P	Mean difference	P	Mean difference	P
E/A ratio	-0.02 (0.3)	0.55	-0.2 (0.4)	**0.03**	-0.1 (0.3)	0.1
LAV (ml)	6.5 (13.6)	0.57	7.0 (18.5)	**<0.05**	3.2 (6.3)	0.07
LAV index (ml/BSA)	3.2 (6.3)	0.92	2.9 (6.8)	**<0.05**	0.2 (7.6)	0.21
Post-bariatric surgery, N=18						
	T 1 vs 2		T 1 vs 3		T 2 vs 3	
	Mean difference	P	Mean difference	P	Mean difference	P
E/A ratio	-0.1 (0.3)	0.68	-0.2 (0.3)	**0.04**	-0.2 (0.2)	0.1
LAV (ml)	2.7 (6.8)	0.17	2.6 (17.5)	0.07	1.4 (3.6)	0.53
LAV index (ml/BSA)	1.4 (3.6)	0.51	1.5 (5.1)	0.09	0.1 (8.8)	0.49

BSA, body surface area*; E/A ratio*, mitral inflow E-wave/A-wave filling; *LAV*, left atrial volume

Mixed model analysis was used to compare the systolic and diastolic function between groups at each trimester and overall, after adjustment for age, race, gestational age, diabetes status and smoking. The overall group comparison across all trimesters is given in Table 3.12 and the estimated marginal means at each trimester for each group is given in Table 3.13.

Table 3.12. Multilevel linear mixed-effects models for systolic, diastolic and longitudinal, function, overall group comparison across all trimesters.

Overall group comparisons (All trimesters)		
	Mean Difference No-surgery – Post-bariatric surgery (95% Confidence Interval for Difference)	**P**
Systolic function		
EDV (mm)	4.706 (-0.922-10.334)	**0.01**
EDV index (mm/BSA)	-1.561 (-4.021-0.898)	0.21
ESV (mm)	3.062 (0.272-5.851)	**0.03**
ESV index (mm/BSA)	-0.068 (-1.298-1.161)	0.91
EF (%)	-0.668 (-2.167-0.831)	0.38
TDI s' (cm)	0.056 (-0.798-0.909)	0.9
Diastolic function		
E/A ratio	-0.271 (-0.37-(-0.172))	**<0.001**
E' lateral (m/s)	-1.806 (-2.773-(-0.838))	**<0.001**
E' medial (m/s)	-1.303 (-2.024-(-0.583))	**<0.001**
E/ E' ratio	0.664 (0.099-1.23)	**0.02**
LAV (ml)	6.255 (2.592-9.918)	**<0.01**
LAV index (ml/BSA)	0.578 (-1.122-2.277)	0.5

BSA, body surface area*; E/A ratio*, mitral inflow E-wave/A-wave filling; *E' lateral*, tissue Doppler imaging E prime measured at lateral mitral annulus; *E' medial*, tissue Doppler imaging E prime measured at medial mitral annulus; *E/E' ratio*, E-wave mitral inflow/ mean E' lateral and E' medial; *EF*, ejection fraction; *EDV*, end-diastolic volume; *ESV*, end-systolic volume; *LAV*, left atrial volume; *TDI s'*, tissue Doppler imaging s' at the lateral tricuspid annulus

Table 3.13. Multilevel linear mixed-effects models for systolic, diastolic and longitudinal function. Estimated marginal means (95% CI) for each trimester and group are given.

	1st Trimester 11-14 weeks			2nd Trimester 20-24 weeks			3rd Trimester 30-32 weeks		
	No-surgery N=20	**Post-bariatric surgery N=20**	**P**	**No-surgery N=33**	**Post-bariatric surgery N=33**	**P**	**No-surgery N=30**	**Post-bariatric surgery N=30**	**P**
Systolic function									
EDV (mm)	95.3 (83.8 -106.8)	93.1 (81.8 -104.4)	0.78	99.8 (90.1 -109.5)	95.1 (84.8 -105.4)	0.32	103.8 (93.7 -113.8)	96.6 (85.8 -107.4)	0.12
EDV index (mm/BSA)	41.7 (36.6 -46.7)	44.4 (39.4 -49.3)	0.19	43.8 (39.6 -48.1)	45.5 (41 -50)	0.37	45.5 (41.3 -49.7)	45.8 (41.3 -50.3)	0.97
ESV (mm)	37.6 (32.1 -43.2)	35.4 (30 -40.8)	0.49	40.3 (35.1 -45.5)	37.2 (31.7 -42.7)	0.23	42.9 (37.7 -48.1)	39 (33.4 -44.6)	0.10
ESV index (mm/BSA)	16.5 (14 -18.9)	16.9 (14.5 -19.3)	0.43	17.7 (15.4 -20)	17.8 (15.4 -20.3)	0.89	18.9 (16.7 -21.2)	18.5 (16.1 -20.9)	0.57
EF (%)	60 (57 -63)	61 (58.1 -64)	0.72	59.3 (56.6 -62)	60.7 (57.8 -63.6)	0.23	59.9 (57.1 -62.7)	59.4 (56.4 -62.4)	0.77
TDI s' (cm)	13.3 (11.6 -15)	13.2 (11.5 -14.8)	0.86	13.5 (12.2 -14.8)	13.9 (12.4 -15.3)	0.58	13.3 (11.9 -14.6)	12.9 (11.4 -14.3)	0.60
Diastolic function									
E/A ratio	1.2 (1 -1.4)	1.6 (1.3 -1.7)	**<0.01**	1.2 (1.1 -1.4)	1.5 (1.3 -1.7)	**<0.001**	1.1 (0.9 -1.3)	1.4 (1.2 -1.5)	**<0.001**
E' lateral (m/s)	15 (13 -17)	17 (15.1 -19)	**0.02**	13.7 (12 -15.3)	15.9 (14.2 -17.7)	**0.01**	12.7 (11 -14.3)	13.8 (12 -15.5)	0.16
E' medial (m/s)	9.1 (7.7 -10.4)	10.7 (9.3 -12.1)	**0.02**	9.1 (7.9 -10.3)	10.3 (9 -11.5)	**0.03**	8.1 (6.9 -9.4)	9.2 (7.9 -10.5)	0.12
E/ E' ratio	6.9 (6 -7.9)	6.2 (5.3 -7.2)	0.16	7.6 (6.7 -8.5)	7 (6 -7.9)	0.10	7.7 (6.7 -8.8)	7.1 (6 -8.2)	0.29
LAV (ml)	59.9 (52.3 -67.5)	54.5 (47.2 -61.9)	0.17	65 (58.7 -71.3)	58.5 (51.8 -65.2)	**<0.05**	66.3 (60.3 -72.3)	59.4 (52.8 -66)	**0.02**
LAV index (ml/BSA)	26.3 (22.8 -29.7)	25.7 (22.4 -29.1)	0.78	28.3 (25.4 -31.3)	28 (24.8 -31.1)	0.85	29.2 (26.2 -32.2)	28.4 (25.1 -31.6)	0.58

BSA, body surface area*; E/A ratio*, mitral inflow E-wave/A-wave filling; *E' lateral*, tissue Doppler imaging E prime measured at lateral mitral annulus; *E' medial*, tissue Doppler imaging E prime measured at medial mitral annulus; *E/E' ratio*, E-wave mitral inflow/ mean E' lateral and E' medial; *EF*, ejection fraction; *EDV*, end-diastolic volume; *ESV*, end-systolic volume; *LAV*, left atrial volume; *LVEF*, left ventricle ejection fraction; *TDI s'*, tissue Doppler imaging s' at the lateral tricuspid annulus

Within both groups, the end-diastolic volume (EDV) and end systolic volume (ESV) trended upwards with a slight decreasing trend in the EF however, there were no significant changes during gestation. When comparing the groups in the overall analysis, EDV and ESV were significantly lower in the post-bariatric group (Table 3.12, Figures 3.9, 3.10), however this difference did not remain after correction for body surface area (BSA) (Table 3.12). There were no significant differences between the trimesters or groups for TDI s' at the right lateral annulus.

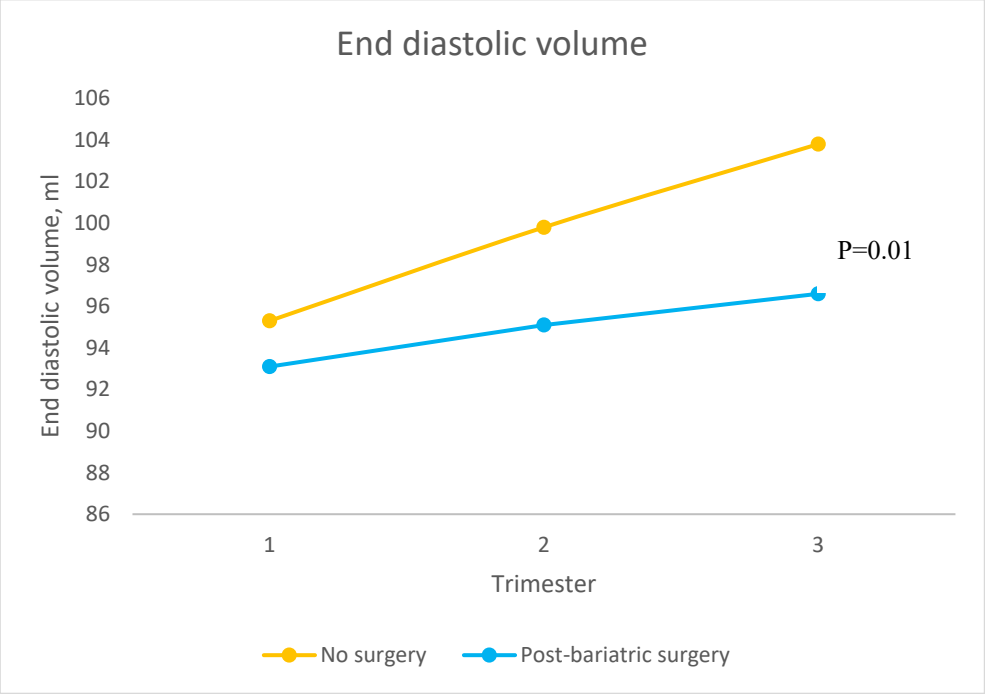


Figure 3.9. Mixed model analysis for end diastolic volume across trimesters in both groups examined.

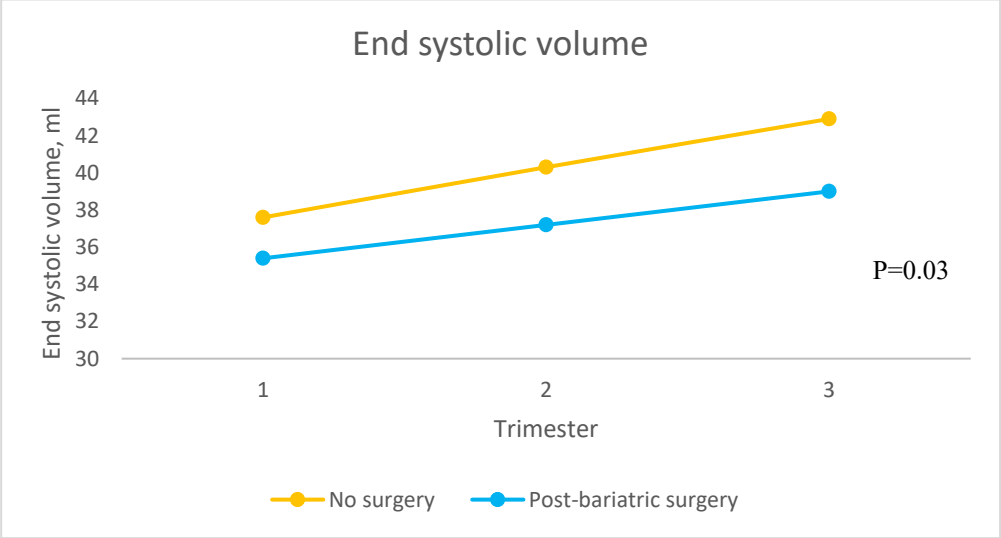


Figure 3.10. Mixed model analysis for end systolic volume across trimesters in both groups examined.

Within both groups the E/A ratio reduced through the trimesters and when comparing the groups, the E/A ratio was higher in the post-bariatric group compared to the no-surgery group in all trimesters (Table 3.12, Figure 3.11).

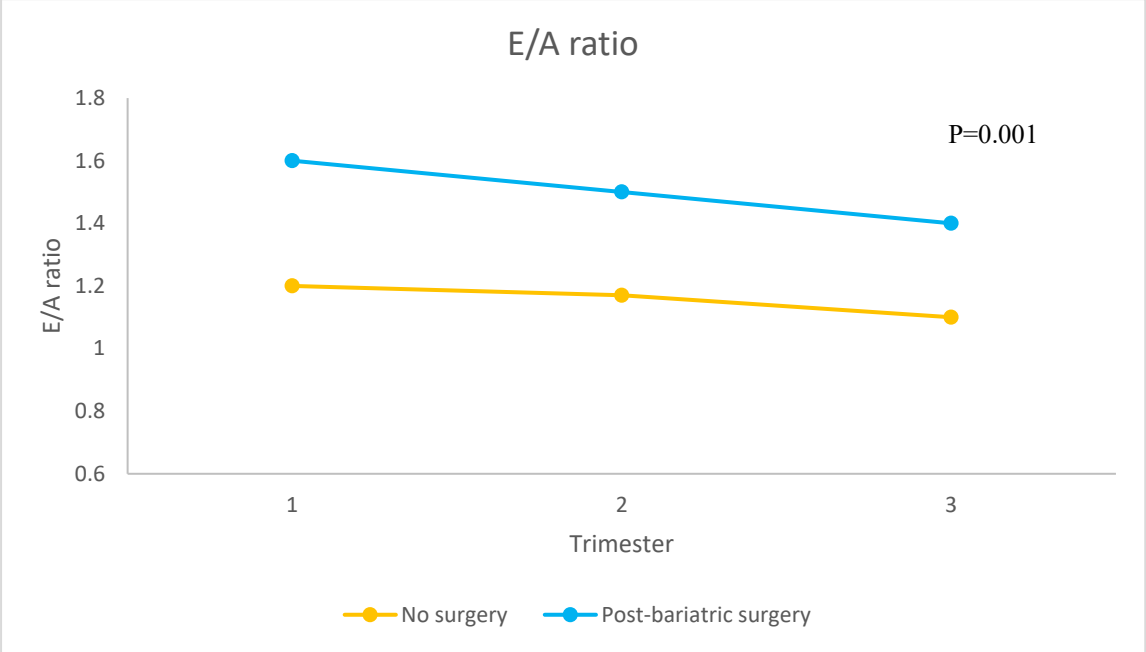


Figure 3.11. Mixed model analysis for mitral inflow E-wave/A-wave ratio across trimesters in both groups examined.

Tissue Doppler indices, E' lateral and E' medial did not change significantly during gestation, when comparing the groups, E' lateral and E' medial were higher and E/E' ratio was lower in the post-bariatric compared to the no-surgery group in the overall analysis (Table 3.12, Figure 3.12).

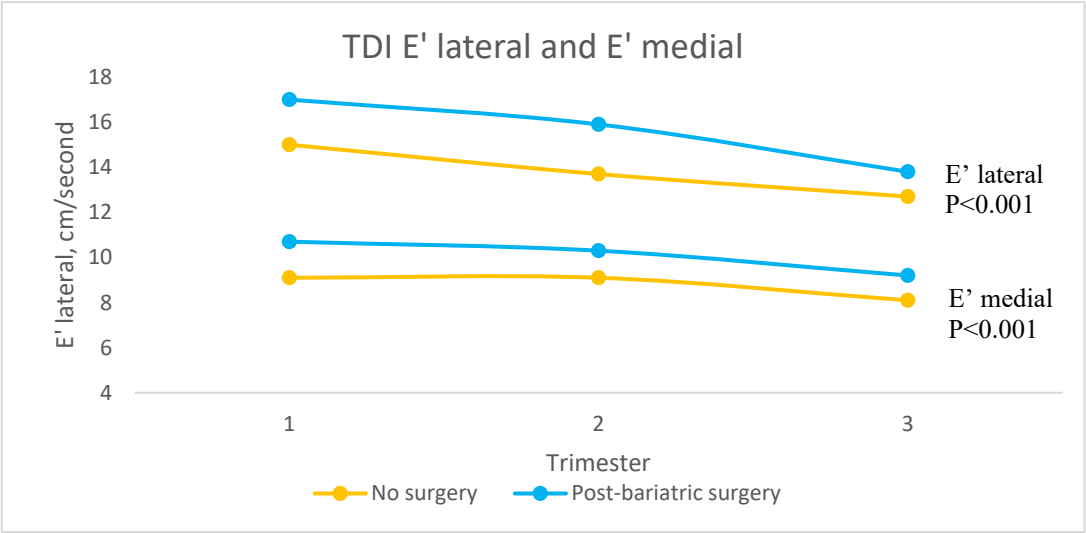


Figure 3.12. Mixed model analysis for tissue Doppler imaging (TDI) E' lateral and E' medial mitral annulus across trimesters in both groups examined.

Within groups, the LA volume trended upwards across the trimesters and was significant in the no-surgery group. In the overall analysis the LA volume was significantly lower in the post-bariatric compared to the no-surgery group (Figure 3.13) although this did not persist after correction for BSA (Table 3.12). There was no significant change in MAPSE or TAPSE during gestation within either group or between groups.

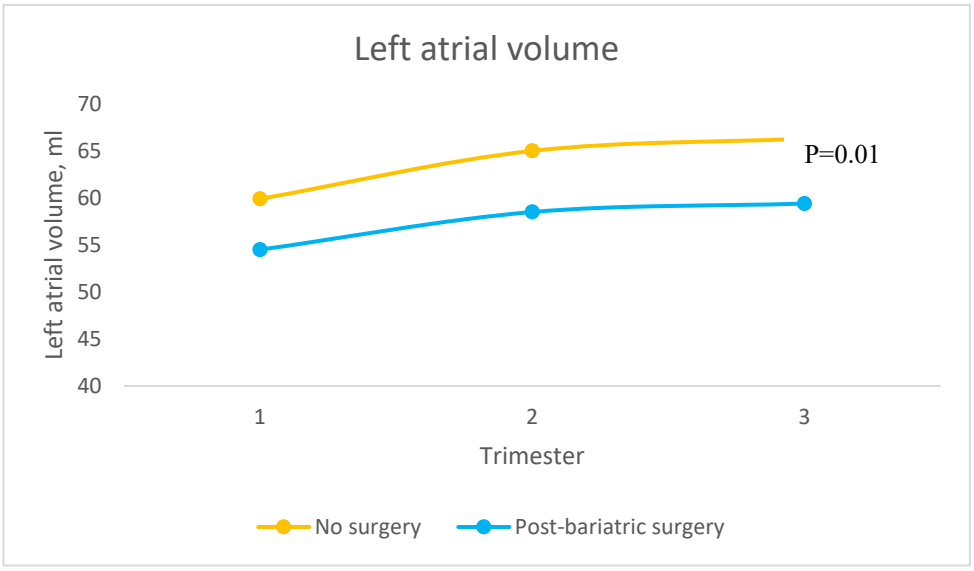


Figure 3.13. Mixed model analysis for left atrial volume across trimesters in both groups examined.

Global longitudinal and circumferential strain

A subgroup of 15 women in each group (no-surgery and post-bariatric) with adequate image quality were used for strain analysis. The mean (standard deviation) in each trimester and comparisons between the groups are given in Table 3.14. Within each group there was no significant difference between the trimesters.

Table 3.14. Global longitudinal strain and global circumferential strain, mean (standard deviation) for each trimester and group with p values of group comparison.

	1st Trimester		
	No-surgery	Post-bariatric surgery	P
GLS	-16.8(3.1)	-17(2.5)	0.89
GCS	-23(4.1)	-22.7(5.5)	0.35
	2nd Trimester		
	No-surgery	Post-bariatric surgery	P
GLS	-15.7(4.3)	-17.6(2.9)	0.16
GCS	-21.0(4.3)	-21.8(3.6)	0.5
	3rd Trimester		
	No-surgery	Post-bariatric surgery	P
GLS	-15.4(3.7)	-18(3.5)	0.09
GCS	-18.8(4.1)	-22.1(3.5)	0.05

GCS global circumferential strain; *GLS*, global longitudinal strain

Mixed model analysis was used to compare the GLS and GCS between groups at each trimester and overall, after adjustment for age, race, gestational age, GDM and smoking. The overall comparison is given in Table 3.15 and the estimated marginal means at each trimester with group comparison is given in Table 3.16. The overall analysis found that GLS was lower in the post-bariatric group compared to the no-surgery group.

Table 3.15. Multilevel linear mixed-effects models for global longitudinal strain and global circumferential strain, overall group comparison across all trimesters

Overall group comparisons (All trimesters)		
	Mean Difference No-surgery – Post-bariatric surgery (95% Confidence Interval for Difference)	**P**
GLS	2.20 (0.56-3.85)	**<0.01**
GCS	1.64 (-0.73-4)	0.17

GCS global circumferential strain; *GLS*, global longitudinal strain

Table 3.16. Multilevel linear mixed-effects models for global longitudinal strain and global circumferential strain. Estimated marginal means (95% CI) for each trimester and group are given.

	1st Trimester			**2nd Trimester**			**3rd Trimester**		
	No-surgery	**Bariatric surgery**	**P**	**No-surgery**	**Bariatric surgery**	**P**	**No-surgery**	**Bariatric surgery**	**P**
GLS (%)	-15.1 (-19-(-13.1))	-16.6 (-19.5-(-13.6))	0.58	-14.4 (-17.7- (-11.2))	-17.3 (-20.3-(-14.4))	0.08	-14.4 (-17.7-(-11.1))	-17.6 (-20.8- (-14.3))	0.06
GCS (%)	-23.1 (-27.7-(-18.5))	-22.88 (-27.4-(-18.))	0.59	-22.33 (-26.9-(-17.7))	-21.9 (-26.6-(-19.2))	0.76	-19.7 (-23.8- (-15.7))	-23.3 (-28.0-(-20.4))	**0.03**

GCS global circumferential strain; *GLS*, global longitudinal strain

Birthweight

The birthweight percentiles in both groups examined are given with maternal characteristics in Table 3.1. We then examined whether maternal cardiovascular parameters including MAP, CO and TPR correlate with BW percentile (Table 3.17, Figures 3.14-3.19).

Table 3.17. Pearson's correlation (R) of birth weight percentile and cardiac output, total peripheral resistance and mean arterial pressure in each group and trimester with p values.

		No-surgery N=33		**Post-Bariatric surgery N=33**	
	Trimester	**R**	**P**	**R**	**P**
Log10 CO	1	0.46	**0.01**	0.08	0.75
	2	0.52	**<0.01**	0.05	0.78
	3	0.51	**<0.01**	0.16	0.38
Long10 TPR	1	-0.49	**<0.01**	-0.01	1.00
	2	-0.63	**<0.01**	-0.07	0.70
	3	-0.48	**<0.01**	-0.08	0.66
Log10 MAP	1	-0.09	0.63	0.05	0.84
	2	-0.27	0.13	0.06	0.73
	3	-0.05	0.81	0.24	0.19

CO, cardiac output; *MAP*, mean arterial pressure; *TPR*, total peripheral resistance

We found a positive significant correlation between CO and BW and a negative significant correlation between TPR and BW in the no-surgery group (Figure 3.14-3.19). In the post-bariatric women, we did not find significant correlations. In either group, we did not find any significant correlation between MAP and BW.

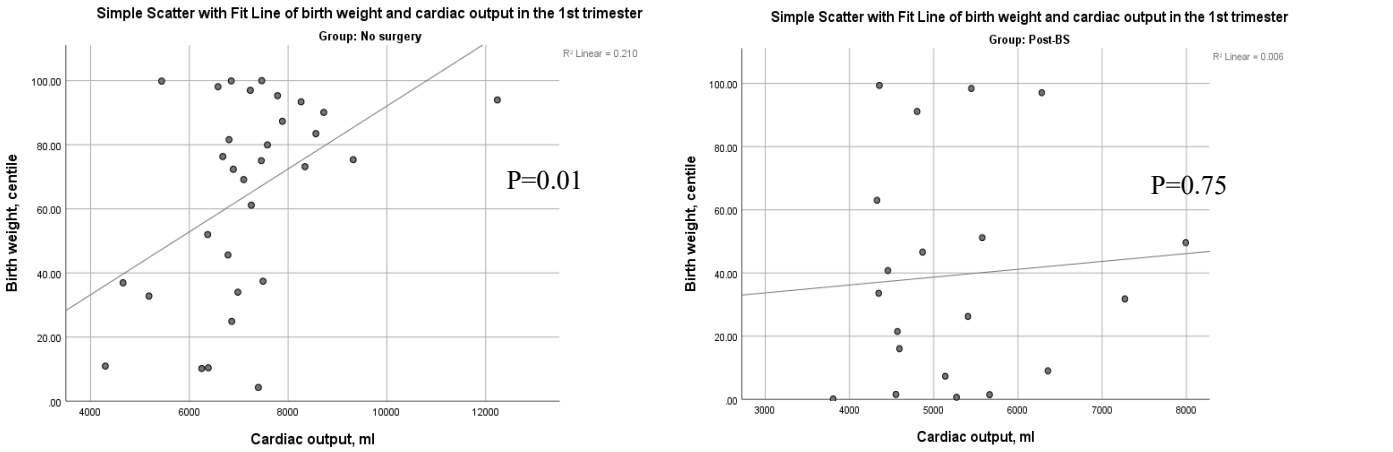


Figure 3.14. Correlation of maternal cardiac output and birth weight percentile in the first trimester in the no-surgery group (left) and post-bariatric surgery group (right)

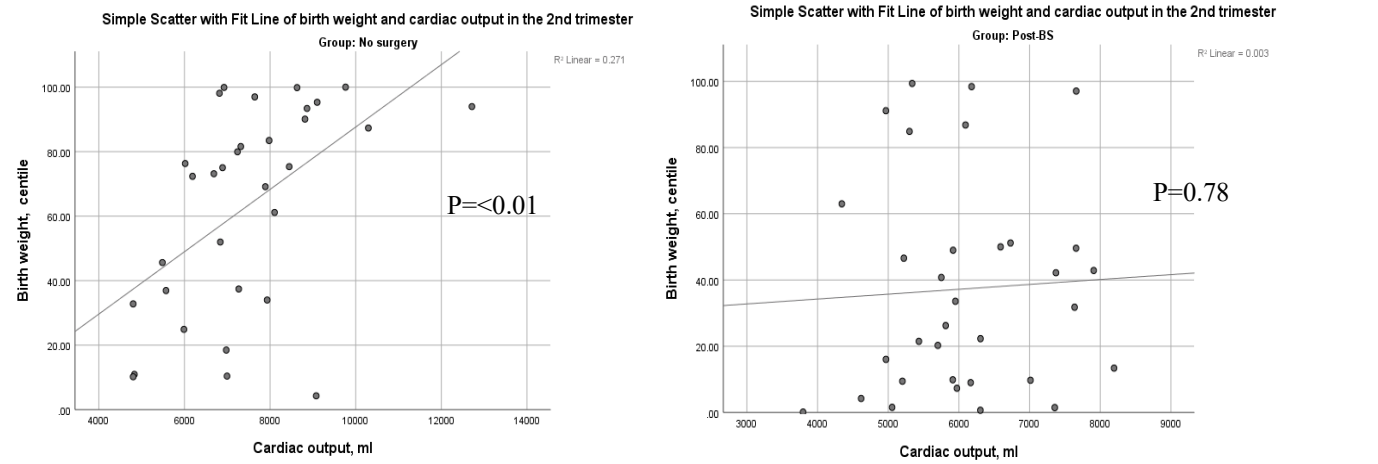


Figure 3.15. Correlation of maternal cardiac output and birth weight percentile in the second trimester in the no-surgery group (left) and post-bariatric surgery group (right)

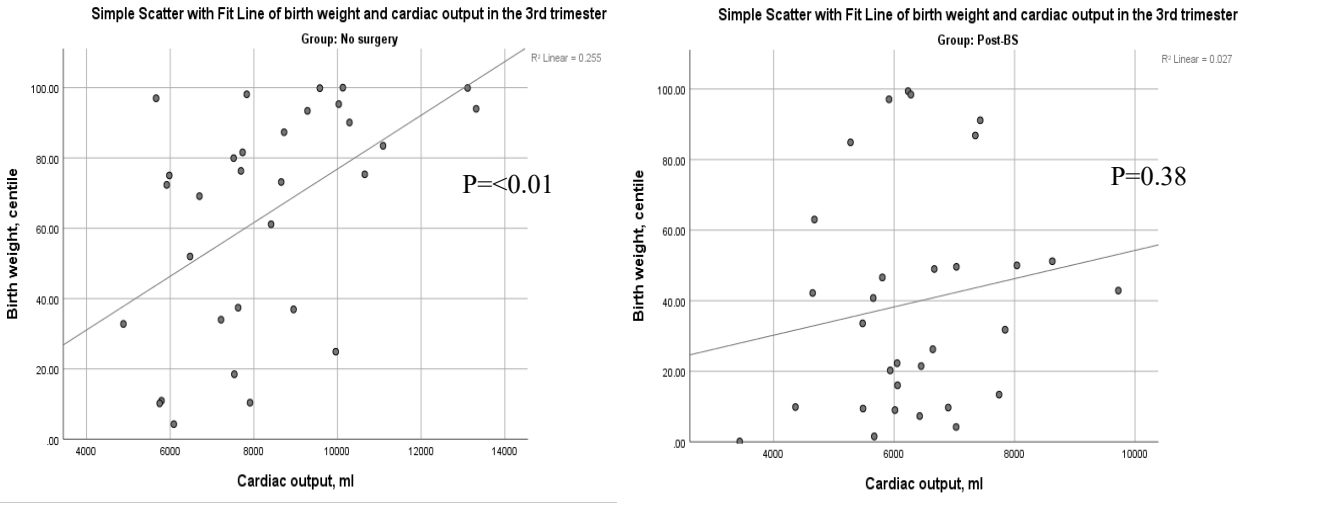


Figure 3.16. Correlation of maternal cardiac output and birth weight percentile in the third trimester in the no-surgery group (left) and post-bariatric surgery group (right)

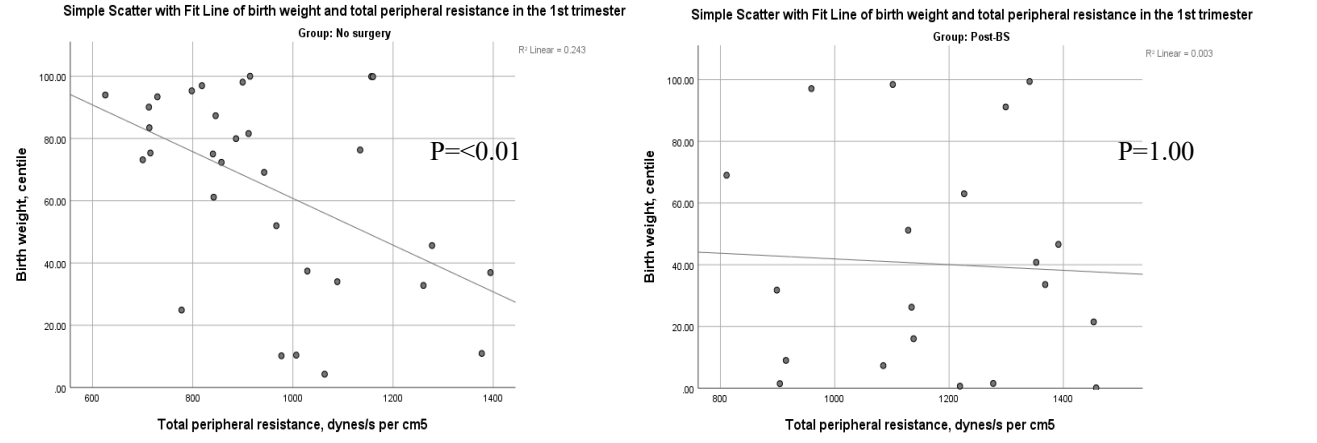


Figure 3.17. Correlation of maternal total peripheral resistance and birth weight percentile in the first trimester in the no-surgery group (left) and post-bariatric surgery group (right)

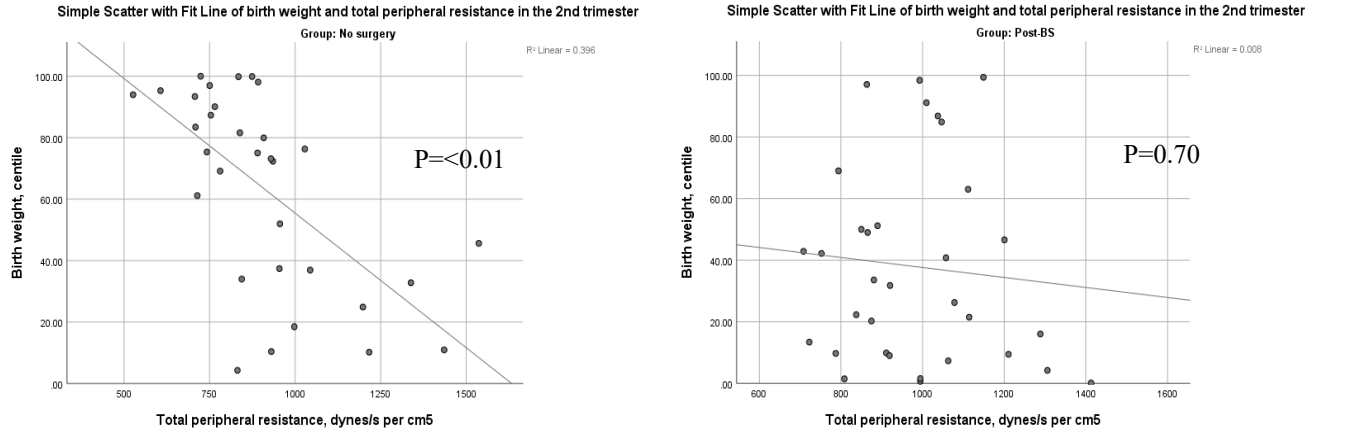


Figure 3.18. Correlation of maternal total peripheral resistance and birth weight percentile in the second trimester in the no-surgery group (left) and post-bariatric surgery group (right)

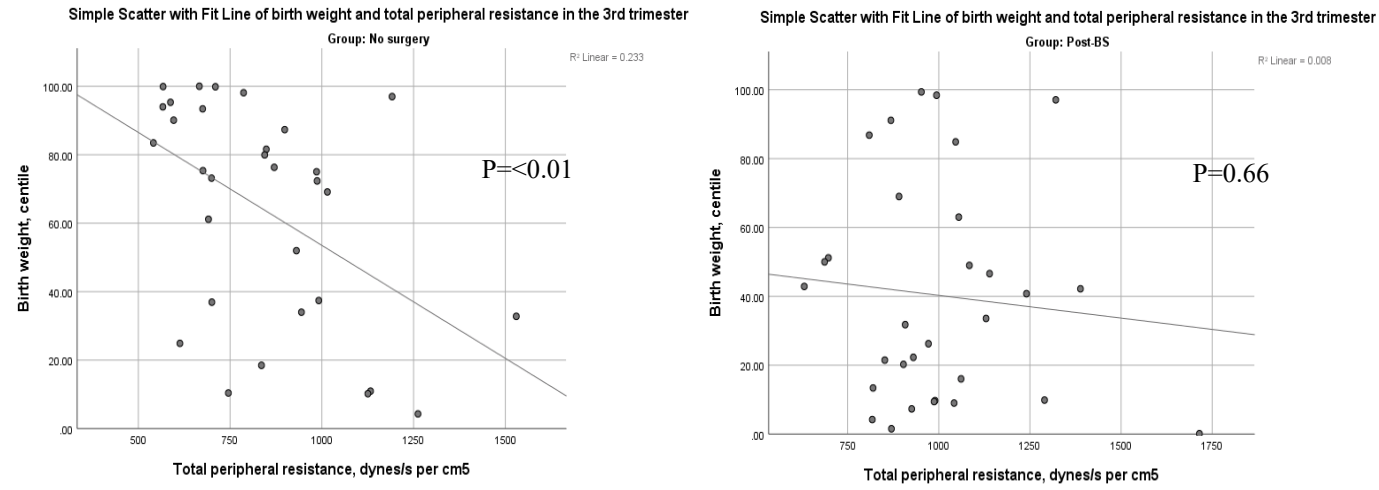


Figure 3.19. Correlation of maternal total peripheral resistance and birth weight percentile in the third trimester in the no-surgery group (left) and post-bariatric surgery group (right)

Discussion

Our study has found significant differences between the groups in maternal haemodynamic function, cardiac geometry and systolic and diastolic function. Maternal blood pressure, HR and CO were lower and TPR higher in the post-bariatric group. In the same group, maternal cardiac geometry differed with lower LV mass and RWT, in addition diastolic indices were more favourable with higher E/A ratio, TDI E' lateral and medial and lower E/E' ratio and LA volume. There was no difference in systolic function measured by EF, however, GLS was lower in the post-bariatric group indicating better systolic function.

Traditionally, hypertension in obesity is related to excess plasma volume expansion and increased CO due to excess body mass, with a concomitant decrease in natriuresis. The raised CO leads to glomerular hyperfiltration and in turn raised distal tubular sodium delivery. Complex mechanisms lead to the upregulation of the renin-angiotensin-aldosterone system and stimulation of the sympathetic nervous system (SNS), which lead to increased sodium reabsorption, plasma volume expansion and arterial hypertension. More recently it has been suggested that hormonal factors may play a role and studies have found a reduction or resolution in hypertension after bariatric surgery usually due to a combined effect of weight loss and gut hormone manipulation. (10) Insulin, leptin, aldosterone and GLP-1 are all known to be involved in BP control. (153) Obese individuals are resistant to leptin with regard to appetite, but hyperleptinemia can stimulate sympathetic activity and the effects on the kidney may influence the BP, similarly, hyperinsulinaema has a direct effect on the SNS. (153)

Aldosterone is known to modulate vascular tone, possibly by increasing the pressor response to catecholamines and impairing the vasodilatory response to acetylcholine. (154) GLP-1 infusion has been shown to increase sodium excretion and also reduced hydrogen secretion, suggesting that GLP-1 might exert its renal effects by directly influencing the natrium-hydrogen exchanger at the proximal tubule of the nephron. (153) Several studies have shown that higher maternal BP in the first trimester of pregnancy is linked to higher risk of developing hypertensive disorders later on in pregnancy. (62) Based on that, it would have been reasonable to assume that the lower maternal BP found in post-bariatric women is likely to be associated with the lower risk of developing hypertensive diseases later on in pregnancy, documented in this population. (111, 155)

Heart rate increased with gestation in both groups, as expected (33) and was consistently lower in the post-bariatric compared to the no-surgery group with similar pre-surgery BMI. Obesity is associated with an imbalance between the sympathetic and para-sympathetic parts of the autonomic nervous system, increased sympathetic outflow can result in raised HR, BP, and microvasculature tone. (156) In studies outside of pregnancy it has been reported that after bariatric surgery, HR is lower and HR recovery after exercise is improved. (157-159) The increase in HR along with SV resulted in an increase in CO in both groups across gestation suggesting that in both groups there is a normal maternal haemodynamic adaptation to pregnancy. (37) When comparing the groups, women with previous bariatric surgery had lower SV, HR and CO. The reduction in these haemodynamic indices is likely to be due to the combined effect of weight loss resulting in a reduced circulating volume, substantial decrease in SNS activity and improvement in cardiac and sympathetic baroreflex function. (160) Outside pregnancy, studies before and after bariatric surgery show a lower CO after surgery in keeping with our finding. (102, 161) Of note, the CO in the post-bariatric group was approaching that of a normal BMI pregnant woman. (72, 162-164) The TPR trended downwards across trimesters in both groups and was significantly lower in the third compared to first trimester which is in keeping with physiological pregnancy changes. (165) When comparing the groups across all trimesters in the overall analysis, the TPR was significantly higher in the post-bariatric group and similar to that of normal BMI pregnancies reported in the literature. (33, 74)

With regard to cardiac geometry, LV mass increased during gestation which is consistent with physiological pregnancy changes. (37, 166) The IVS, PW diameter, LV mass and RWT were significantly lower in the post-bariatric compared to the no-surgery group with similar pre-

surgery BMI. Our findings are in keeping with reported changes in cardiac geometry after bariatric surgery. (91, 102, 167) The traditional haemodynamic model in obesity describes increased stroke workload owing to an increased preload and SV leading to left ventricular dilatation, which in turn causes a rise in wall stress and increasing myocardial mass to compensate. Eccentric hypertrophy follows with subsequent left ventricular diastolic and sometimes systolic dysfunction. In recent years it is thought that early hypertrophic changes of the heart are secondary to obesity-associated hyperleptinaemia and the subsequent cardiac dilatation seen in morbid obesity is likely volume-induced. It has been shown that leptin causes hypertrophy and the weight loss achieved by bariatric surgery decreases leptin levels significantly. (92, 93, 168) In our study, the no-surgery group showed a tendency towards concentric LV remodelling (RWT=0.40), which was not the case for the post-bariatric group (RWT=0.36).

With regard to systolic function, maternal EDV and ESV trended upwards in both groups, with a slight decreasing trend in the EF however, there were no significant differences. Similarly, in literature it is reported that maternal EDV and ESV have a non-significant increase in pregnancy. (169) Changes in EF in pregnancy vary in studies with most of them suggesting no change. (33, 37, 169) Despite the lack of difference in EF, GLS was lower in the post-bariatric group suggesting better systolic function compared to the no-surgery group with similar pre-surgery BMI. Global longitudinal strain has been shown to have increased sensitivity and specificity in predicting cardiovascular outcomes across various cardiac pathologies and GLS use clinically can identify subclinical left ventricular systolic dysfunction where EF is normal.(170)

As far as the diastolic indices is concerned, we found that the E/A ratio reduced across gestation in both groups, as expected (37) and was higher in the post-bariatric compared to the no-surgery group with similar pre-surgery BMI suggesting better mitral filling in the former group. Diastolic dysfunction including lower E/A ratio has been reported in obese pregnant women suggesting a maladaptation to pregnancy. The post-bariatric pregnant women had better diastolic function, as suggested by the higher E/A ratio, E' lateral and medial and the lower E/E' ratio and LA volume. Similar to our findings but outside the setting of pregnancy, it has been reported that E/A ratio, TDI E' lateral and medial are higher and E/E' ratio and LA volume lower after bariatric surgery. (18, 171) Diastolic dysfunction in obesity is related to a hyperdynamic circulation due to increased preload as well as afterload due to arterial stiffness, leading to left ventricular hypertrophy, reduced compliance and altered LV filling patterns. The

improvement in diastolic indices is likely to be due to a combined effect of weight loss, reducing the circulating load, and the added benefit of gut hormone changes such as reduced leptin induced hypertrophy. (91, 93)

We found that the post-bariatric group had a significantly lower BW percentile compared to the no-surgery group with similar pre-surgery BMI which is in keeping with studies that have reported smaller babies in women after bariatric surgery. (111) It is thought that this may be due to the therapeutic post-surgical state of maternal malnourishment and micronutrient deficiencies or the relatively lower maternal glucose availability. (172) In the no-surgery group, we found a positive correlation between maternal CO and BW and a negative correlation between TPR and BW. Our findings are consistent with other studies demonstrating similar trends and a close association between maternal CO and fetal growth and BW. (58, 59)

In pathological pregnancy the maternal cardiovascular function has been shown to play an important role with studies reporting a hyperdynamic circulation of high CO in both the clinical and preclinical phase of the PE.(56, 173) We have found that women with previous bariatric surgery have a lower CO and BP and this could mean they are less prone to develop hypertensive disorders in pregnancy. (111) In addition, changes in LV geometry and diastolic function have been reported in the physiological as well as pathological adaptation to pregnancy. (37, 53) Left ventricle concentric remodelling and diastolic dysfunction have been reported in study of mid-trimester pregnant women who subsequently went on to develop PE. (53) In recent years there has been growing interest in the maternal cardiovascular function as a precursor of hypertensive disease in pregnancy (47, 55); our findings of lower CO, BP and LV mass/RWT with more favourable diastolic and systolic indices, may explain why women with previous bariatric surgery have a lower incidence of hypertensive disease in pregnancy.

This study provides novel data on detailed cardiovascular assessments in women with previous bariatric surgery and, to our knowledge, this has not been previously investigated. However, there are limitations to our study design as previous studies outside of pregnancy examined the same individuals before and after surgery. This was not feasible in our pregnant population so we found a pregnant population that was as matched as closely as possible to the pre-surgery status of the post-bariatric women with regards to age, race, BMI and diabetes status.

Conclusion

This study has found significant differences between the groups in haemodynamic function, cardiac geometry and systolic and diastolic function. The findings suggest a more optimal cardiovascular adaptation to pregnancy in women with previous bariatric surgery compared to women without surgery and may be associated with the reduced prevalence of hypertensive disorders in pregnancy seen in the former population.

Chapter 4

Maternal cardiovascular adaptation in pregnancy in women with previous bariatric surgery compared to women with a similar early pregnancy BMI

Abstract

Background: As the obesity epidemic grows, bariatric surgery is becoming more common in the management of obesity. Outside of pregnancy bariatric surgery is known to have several positive cardiovascular implications, not only through weight loss, but also mediated through the cardio-enteric axis. In pregnancy, the cardiovascular adaptation is vital in maintaining a healthy pregnancy and maladaptation has been associated with hypertensive disease. Studies have shown that late pre-eclampsia is associated with a high cardiac output in the pre-clinical and clinical phase. Pregnancy after bariatric surgery associated with a reduced risk of hypertensive disorders, however, the maternal cardiovascular system after bariatric surgery has not been previously investigated.

Objective: To investigate the maternal cardiovascular adaptation to pregnancy in women with previous bariatric surgery compared to women with a similar early pregnancy body mass index (BMI) but no history of weight loss surgery.

Methods: This was a prospective, observational, longitudinal study. Participants were seen at three time points in pregnancy; 12-14, 20-24 and 30-32 weeks. Women with previous bariatric surgery were compared to women without surgery but with similar early pregnancy and also matched for maternal age, race and gestational diabetes. At each time point blood pressure (BP) was measured twice and the mean value was recorded. Maternal cardiac function was assessed using transthoracic echocardiography. Multilevel linear mixed-effects models were used for all the comparisons.

Results: The study included 41 pregnant women with and 41 without previous bariatric

surgery. Overall, the maternal systolic and diastolic BP, heart rate and cardiac output were lower in the post-bariatric women compared to the no-surgery group ($p<0.01$ for all comparisons). There was no significant difference in ejection fraction between groups, however, there was lower global longitudinal ($p<0.01$) and circumferential strain in the post-bariatric group ($p=0.02$), suggesting better systolic function. There was evidence of more optimal diastolic indices in the post-bariatric group with a higher E/A ratio ($p<0.001$), TDI E' lateral ($p<0.01$)/medial ($p=0.03$) and lower left atrial volume ($p<0.05$).

Conclusions: Our findings suggest a more optimal cardiovascular adaptation to pregnancy in women after bariatric surgery. As our groups were matched for early pregnancy BMI, it is unlikely that the improved maternal cardiac performance is due solely to the weight loss and indicates influence from the metabolic alterations as a result of the surgery. Studies of pregnancy after bariatric surgery report lower rates of pre-eclampsia. The reasons of this improvement are largely unknown. Bariatric surgery is associated with a lower maternal cardiac output and BP, it would be reasonable to postulate that these haemodynamic alterations play an important role in the lower prevalence of hypertensive disorders in pregnancy reported in this population. This can inform national guidance regarding beneficial effects of bariatric surgery in obese women of reproductive age contemplating pregnancy.

Introduction

The obesity epidemic is growing and has significant chronic health implications. (3) Obesity has several effects on the cardiovascular system. Hemodynamically, there is increased cardiac output (CO) as a result of increased stroke volume (SV) and heart rate (HR). The geometry is altered with left arial (LA) enlargement and left ventricle (LV) hypertrophy compared to individuals of normal BMI. Diastolic function can be impaired however systolic function is usually preserved. (6, 19) Bariatric surgery is a successful treatment for sustainable weight loss which achieves around 55% excess body weight loss across different surgical methods. (78, 79) Studies of cardiovascular function after bariatric surgery have found reduced hypertension, changes in cardiac geometry and improvement in diastolic function. (10, 91)

Traditionally, it was thought that cardiac remodelling after bariatric surgery was solely due to haemodynamic changes, such as lowering of the BP and weight loss. However, there is now

evidence that manipulation of enteric gut hormones contributes to beneficial cardiovascular effects via the entero-cardiac axis. (91) It has been reported that BP is lowered as early as 10 days post-bariatric surgery where weight loss is relatively limited. (89, 90)

Pregnancy is associated with significant maternal cardiovascular and haemodynamic changes to support the gravid uterus and fetal development. Systemic vasodilation leads to a reduction in total peripheral resistance (TPR) and an increase in SV and CO. (28) Maternal cardiovascular adaptation to pregnancy has been implicated in the pathophysiology of pregnancy complications such as pre-eclampsia (PE). (45) Late onset PE is associated with high CO and low resistance in the pre-clinical and clinical phase. (54, 56) Similarly, maternal LV remodeling and reduced diastolic indices have been reported in the pre-clinical and clinical phase of the disease. (53, 54)

Obese pregnant women have an altered cardiovascular adaptation to pregnancy with a reported 40% prevalence of diastolic dysfunction and a significant reduction in global longitudinal strain, a sensitive marker of systolic function. (72) A longitudinal study of obese pregnant compared to normal BMI pregnant women found a high volume/low-resistance circulation in the first and second trimester, however, in the third trimester, the CO of obese women decreased which was not true in nonobese women. (74) These differences suggest a maladaptive cardiovascular response to pregnancy. Obesity is associated with late PE and studies have shown that both conditions demonstrate a hyperdynamic circulation with high CO and low resistance. (47, 54, 72)

Several studies have reported that pregnancy following bariatric surgery is associated with a reduced risk of complications, notably hypertensive disorders compared to women with similar pre-surgery and similar early pregnancy BMI. (111) The mechanisms underlying the changes in pregnancy outcomes are largely unknown, however, it is likely the maternal cardiovascular adaptation plays a pivotal role in maintaining a healthy pregnancy and maladaptation has been associated with hypertensive disease. Nevertheless, maternal cardiovascular changes in pregnancies following bariatric surgery compared to women with similar early pregnancy BMI has not been studied before.

Hypothesis

In pregnancies following bariatric surgery, maternal cardiovascular adaptation is altered compared to that of women with similar early pregnancy BMI.

Aim

1. Investigate longitudinally, the maternal cardiovascular adaptation to pregnancy in women following bariatric surgery compared to women with similar early pregnancy BMI. Maternal cardiovascular system will be assessed using 2D echocardiography, including cardiac geometry, haemodynamic variables, systolic, diastolic and longitudinal function.
2. Investigate the association of maternal haemodynamic indices with birth weight.

Methods

This was a prospective, observational, longitudinal study. Pregnant women were recruited from April 2018 to June 2020 at Chelsea & Westminster Hospital, London, UK. Participants were identified through a booking-perinatal database (CIMIS). Following the 1st trimester scan, participants were approached by members of the research team and recruited in the following groups:

- Group 1 – Pregnant women with previous bariatric surgery
- Group 2 – Pregnant women without a history of bariatric surgery matched for early pregnancy BMI, age, race and presence of diabetes

Women who had a singleton pregnancy and attended at least two out of three research visits were included. Participants were seen at three time points during their pregnancy, 12-14 weeks, 20-24 weeks and 30-32 weeks. Women who had bariatric surgery were matched to women without surgery. Matching between the groups was achieved via categories for BMI (20-24.9, 25-29.9, 30-34.9, 35.0-39.9, ≥40), age (20-25, 26-30, 31-35, 25-40, >40), race (white or non-white) and presence of diabetes mellitus.

Maternal characteristics, including age, parity, race, smoking status and medication history were recorded in the research database. Maternal weight was taken to the nearest 0.1 kg using a calibrated electronic scale, with the patient wearing light clothing and no footwear. Height was measured to the nearest 0.5 cm also without footwear. Blood pressure measurements were performed manually using a sphygmomanometer (Accoson Dekamet, AC Cossor & Son (Surgical) Ltd, London, UK) according to the recommendations of the British Hypertension Society. (120) Two readings, 5 minutes apart, were taken in a seated position from the left arm. The mean value was recorded. Maternal cardiovascular system was assessed using 2D echocardiography and cardiac geometry, haemodynamic variables, systolic, diastolic and longitudinal function were evaluated.

Transthoracic echocardiography was performed after a rest period of 10 minutes in the left lateral decubitus position. Two-dimensional, M-mode and tissue Doppler imaging were performed using a Ie33 Philips Ultrasound system according to European and American guidelines. (135, 151) Standard parasternal and apical views were used and digital loops of 3 cardiac cycles with associated electrocardiogram information were stored on to the hard disk of the machine. The methodology used for image acquisition and measurements is described in detail in Chapter 2. Offline analysis was performed according to American and European echocardiography guidelines. (135, 151) On a subgroup of patients, speckle tracking analysis was performed to obtain global longitudinal and circumferential strain (GLS/GCS). Parasternal short axis views and apical 2, 3 and 4 chamber views were analysed using the 2D Cardiac Performance Analysis, TomTec Imaging System, Munich, Germany. The methodology used is described in detail in Chapter 2.

Information on pregnancy outcomes were obtained from the Hospital's perinatal database. Development of gestational diabetes (GDM) and hypertensive disorders of pregnancy were defined as previously described (Chapter 2). Birth weight percentiles were calculated, as previously described (Chapter 2).

Statistical analyses

The statistical analysis is described in further detail in Chapter 2. In brief, the groups were compared at each time point (trimester) and within each group the time points were compared

using the unpaired Student t-test/Mann-Whitney or chi-square ($\chi 2$) for numerical and categorical data respectively. Differences were considered statistically significant at $p<0.05$.

Hierarchical modelling was used for further analysis of haemodynamic, geometric, diastolic and strain imaging variables using multilevel linear mixed-effects models. The fixed effect component included time (the 3 visits), study group, age, race and GDM, smoking, gestation and first-order interaction between time and study group. The correlation of CO, TPR and MAP with birth weight were assessed by Pearson's correlation. All analyses were performed using IBM SPSS Statistics, version 26.0, 2019 (*IBM Corp., Armonk, New York, USA*).

Sample size calculation was performed using the G*Power software (G*Power for Windows Os X, v. 3.1, February 2020, Heinrich-Heine-Universität, Dusseldorf, Germany).(152) There are no previous studies investigating the cardiovascular system pregnant women with previous bariatric surgery. Therefore, it was difficult to be accurate on the number of subjects required in each group to obtain results with adequate power. Using studies of individuals before and after bariatric surgery outside of the context of pregnancy we have estimated sample sizes. To demonstrate a similar effect to Owan et al.(102) in CO and Kaier et al.(108) for mitral inflow E-wave/A-wave (E/A) ratio and global longitudinal strain (GLS) for an alpha = 0.05 and a power of 80%, we would need 14 study subjects in each group and each trimester.

Results

The study included 41 pregnant women post-bariatric surgery and 41 women without surgery matched for early pregnancy BMI, age, race and GDM. The maternal characteristics are given in Table 4.1. In the post-bariatric surgery group, 21 women had undergone a gastric bypass, 13 women had undergone a sleeve gastrectomy and 7 women had undergone gastric band. The mean time interval between surgery and conception was 49.6 months. As expected, there were no significant differences in the maternal demographics between the study groups. None of the women in the post-bariatric group developed hypertensive disorders and these women, overall, delivered smaller babies than the women without surgery.

Table 4.1. Maternal demographic characteristics and pregnancy outcomes of the study participants.

Variable	No-surgery N=41	Post-bariatric surgery N=41	P
Age (years)	33.2 (5.2)	33.6 (5.7)	0.78
Racial group			
White, n (%)	33 (80.5)	34 (82.9)	0.78
Other, n (%)	8 (19.5)	7 (17.1)	
Body mass index at booking (kg/m^2)	34.5 (6.8)	34.3 (7.1)	0.90
Body mass index prior to surgery (kg/m^2)	-	46.5 (7.4)	-
1st Trimester weight (kg)	93 (81.2-113.7)	92.1 (78.5-111.8)	0.72
2nd Trimester weight (kg)	97.2 (84.8-114.6)	99.7 (81.9-115.5)	0.87
3rd Trimester (kg)	99.6 (87.7-121.1)	102 (85.7-117.0)	0.78
Weight change T2-T1	3.1 (1.1-4.4)	3.8 (1.2-4.9)	0.39
Weight change T3-T2	3 (1.4-4.2)	2.9 (0.7-4.8)	0.75
Weight change T3-T1	6 (2.6-7.8)	5.8 (1.3-9.6)	0.90
Parity			
Nulliparous, n (%)	21 (51.2)	23 (56.1)	0.66
Parous, n (%)	20 (48.8)	18 (43.9)	
Conception			
Spontaneous, n (%)	35 (85.4)	39 (95.1)	0.14
Assisted reproductive technology, n (%)	6 (14.6)	2 (4.9)	
Smoking			
No, n (%)	39 (95.1)	37 (90.2)	0.40
Yes, n (%)	2 (4.9)	4 (9.8)	
Hypertensive disorders of pregnancy			
No, n (%)	37 (90.2)	41 (100)	0.04
Yes, n (%)	4 (90.8)	0 (0)	
Gestational diabetes mellitus			
No, n (%)	34 (82.9)	34 (82.9)	1.00
Yes, n (%)	7 (17.1)	7 (17.1)	
Mode of delivery			
Spontaneous vaginal delivery, n (%)	18 (43.9)	20 (48.8)	0.81
Operative vaginal delivery, n (%)	5 (12.2)	3 (7.3)	0.51

Caesarean section, n (%)	18 (43.9)	18 (43.9)	1.00
Gestational age at birth (weeks)	39.1 (38.4-40.4)	38.8 (37.7-39.7)	0.34
Birthweight (g)	3580 (3170-3805)	3110 (2530-3375)	**0.01**
Birth weight percentiles (%)	64 (38.5-84)	29 (6-56.5)	**0.01**

Data are expressed as mean (standard deviation), median (interquartile range) or n (%).
T1, first trimester; *T2,* second trimester; *T3,* third trimester

Hemodynamic variables

The median raw values of the haemodynamic variables in the three trimesters of pregnancy and comparisons between the groups are given in Table 4.2. Within each group the trimesters were compared and for significant differences, the mean difference and p values for trimester 1 vs 2, trimester 1 vs 3 and trimester 2 vs 3 are given in Table 4.3.

Table 4.2. Haemodynamic variables, median (interquartile range) for each trimester and group with p values of group comparison.

	1st Trimester			**2nd Trimester**			**3rd Trimester**		
	No-surgery N=26	**Post-bariatric surgery N=26**	**P**	**No-surgery N=41**	**Post-bariatric surgery N=41**	**P**	**No-surgery N=36**	**Post-bariatric surgery N=36**	**P**
SBP (mmHg)	109.5 (102.4-117)	104.5 (93.8-110.5)	**0.01**	108 (100.5-115)	102.5 (91-110)	**<0.01**	109 (102.6-114.5)	104 (95.8-111)	**0.03**
DBP (mmHg)	61.3 (60-70.3)	61.5 (59.8-67.5)	0.47	63 (59-69.5)	60 (56-63)	**<0.01**	63 (61-68.8)	62 (58-68)	0.24
MAP (mmHg)	77.3 (74.3-84.6)	75.5 (71.9-81)	0.14	79.7 (72.8-84)	74.8 (68.2-78.3)	**<0.01**	78.7 (75.4-83.4)	77.3 (70.3-82.5)	0.14
HR (bpm)	76 (70-84)	73 (66.5-75)	**0.02**	82 (71.5-88)	73 (67.5-80)	**0.01**	89.5 (80-95)	79 (71.5-86)	**0.01**
LVOT VTI (mm)	24.2 (21.6-26.3)	22 (21-24.3)	0.70	24.2 (22-26.1)	23 (21.6-26.6)	0.45	24.9 (21.1-27.7)	23.2 (21.2-25.7)	0.29
SV (ml)	77.1 (69.5-90.5)	72 (66.6-81.3)	0.12	83.6 (70.2-90.4)	81.7 (72.6-87.7)	0.66	82.2 (76.5-93.3)	82.4 (73.7-90.4)	0.74
CO (L/min)	6.1 (5.1-6.9)	5.1(4.5-5.7)	**0.01**	6.7 (6-7.6)	6 (5.3-6.9)	**0.03**	6.7 (5.9-8.5)	6.3 (5.7-7.4)	0.05
TPR (dynes/s per cm^5)	1076 (879.1-1316.7)	1213.8 (1097.3-1343.8)	0.11	935.1 (816-1119.1)	994.2 (856.7-1072.4)	0.61	933.2(751.4-1084.1)	971.5 (868.2-1072.5)	0.38
SVI (mm/BSA)	39 (36.6-42.4)	36.6 (32-39.8)	0.05	40.3 (37.7-45)	39.5 (36.5-44.6)	0.62	40 (35.4-46.3)	40.8 (36.7-47.7)	0.80
CI (mm/BSA)	3 (2.5-3.4)	2.5 (2.3-2.8)	**<0.01**	3.3 (2.9-3.7)	3 (2.7-3.3)	**0.01**	3.3 (2.9-4.2)	3.2 (2.8-3.6)	0.11

BSA, body surface area*; CO*, cardiac output; *CI* cardiac index; *DBP*, diastolic blood pressure; *HR*, heart rate; *LVOT TVI*, left ventricle outflow tract velocity time integral; *MAP*, mean arterial pressure; *SV*, stroke volume; *SVI*, stroke volume index; *SBP*, systolic blood pressure; *TPR*, total peripheral resistance

Table 4.3. Mean difference of haemodynamic variables between trimesters in the two groups of women (actual values given in Table 4.2). All comparisons have been adjusted by the Bonferroni correction for multiple tests. (T1: 11-14 weeks, T2: 20-24 weeks, T3: 30-32 weeks)

No-surgery, N=22						
	T 1 vs 2		T 1 vs 3		T 2 vs 3	
	Mean difference	P	Mean difference	P	Mean difference	P
HR (bpm)	4.8 (10.2)	0.07	8 (10.6)	**0.04**	3.1 (9.8)	0.18
CO (L/min)	0.4 (0.1)	0.06	0.8 (1.7)	**0.02**	0.4 (1.7)	0.54
TPR (dynes/s per cm5)	-45 (268.1)	0.48	-81.9 (279.4)	**0.03**	-36.9 (301.2)	0.85
CI (mm/BSA)	0.2 (0.6)	0.29	3.9 (0.8)	**0.04**	0.2 (0.8)	0.64
Post-bariatric surgery, N=22						
	T 1 vs 2		T 1 vs 3		T 2 vs 3	
	Mean difference	P	Mean difference	P	Mean difference	P
HR (bpm)	3.1 (6)	0.4	7 (10.5)	**0.04**	4 (8.9)	0.16
CO (L/min)	0.7 (0.7)	**0.02**	1.2(1.2)	**<0.001**	0.5 (0.9)	0.13
TPR (dynes/s per cm5)	-192.7 (239.4)	**0.01**	-218.5 (309.2)	**0.02**	-25.8 (187.7)	0.4
CI (mm/BSA)	0.3 (0.3)	**0.02**	0.6 (0.6)	**<0.001**	0.3 (0.4)	0.05

BSA, body surface area*; CO*, cardiac output; *CI* cardiac index; *HR*, heart rate; *TPR*, total peripheral resistance

Mixed model analysis was used to compare the haemodynamic variables between groups at each trimester and overall, after adjustment for age, race, gestational age, diabetes status and smoking. The overall group comparison across all trimesters is given in Table 3.4 and the estimated marginal means at each trimester for each group is given in Table 3.5.

Table 4.4. Multilevel linear mixed-effects models for Log10 haemodynamic variables, overall group comparison across all trimesters

Overall group comparisons (All trimesters)		
	Mean Difference No-surgery – Post-bariatric surgery (95% Confidence Interval for Difference)	**P**
Log10 SBP (mmHg)	0.029 (0.019-0.04)	**<0.01**
Log10 DBP (mmHg)	0.023(0.01-0.036)	**<0.01**
Log 10 MAP (mmHg)	0.026 (0.015-0.036)	**<0.01**
Log10 HR (bpm)	0.035 (0.02-0.05)	**<0.01**
Log10 SV (ml)	0.009 (-0.01-0.029)	0.34
Log10 CO (L/min)	0.045 (0.023-0.067)	**<0.01**
Log10 TPR (dynes/s per cm^5)	-0.019 (-0.042-0.005)	0.12
Log10 SVI (mm/BSA)	0.009 (-0.01-0.028)	0.37
Log10 CI (mm/BSA)	0.044 (0.022-0.065)	**<0.01**

BSA, body surface area*; CO*, cardiac output; *CI* cardiac index; *DBP*, diastolic blood pressure; *HR*, heart rate; *MAP*, mean arterial pressure; *SV*, stroke volume; *SVI*, stroke volume index; *SBP*, systolic blood pressure; *TPR*, total peripheral resistance

Table 4.5. Multilevel linear mixed-effects models for Log10 hemodynamic variables. Estimated marginal means (95% CI) for each trimester and group are given.

	1st Trimester			**2nd Trimester**			**3rd Trimester**		
	No-surgery N=26	**Post-bariatric surgery N=26**	**P**	**No-surgery N=41**	**Post-bariatric surgery N=41**	**P**	**No-surgery N=36**	**Post-bariatric surgery N=36**	**P**
Log10 SBP (mmHg)	2.03 (1.96-2.11)	2.00 (1.93-2.08)	**<0.01**	2.04 (2.02-2.06)	2.01 (1.99-2.03)	**<0.001**	2.06 (2-2.11)	2.03 (1.97-2.09)	**0.01**
Log10 DBP (mmHg)	1.79 (1.70-1.88)	1.78 (1.69-1.86)	0.38	1.81 (1.79- 1.8)	1.78 (1.76-1.80)	**<0.001**	1.84 (1.77-1.91)	1.83 (1.76-1.90)	0.42
Log 10 MAP (mmHg)	1.89 (1.81-1.96)	1.87 (1.79-1.94)	0.09	1.90 (1.89-1.92)	1.87 (1.85-1.89)	**<0.001**	1.93 (1.87-1.98)	1.91(1.85-1.97)	0.11
Log10 HR (bpm)	1.92 (1.81-2.02)	1.88 (1.78-1.99)	**0.03**	1.92 (1.90-1.95)	1.89 (1.86-1.91)	**0.01**	1.93(1.85-2.02)	1.89 (1.81-1.98)	**<0.01**
Log10 SV (ml)	1.73 (1.60-1.87)	1.70 (1.57-1.83)	0.16	1.9 (1.88-1.92)	1.89 (1.86-1.92)	0.79	2.04 (1.96-2.13)	2.02 (1.91-2.13)	0.98
Log10 CO (L/min)	3.65 (3.50-3.80)	3.58 (3.44-3.73)	**<0.01**	3.81 (3.78-3.85)	3.78 (3.74-3.81)	**0.04**	3.95 (3.83-4.07)	3.91 (3.79-4.03)	**0.04**
Log10 TPR (dynes/s per cm^5)	3.14 (2.97-3.30)	3.18 (3.02-3.33)	0.08	3.00 (2.96-3.03)	3.00 (2.96-3.03)	0.89	2.89 (2.76-3.01)	2.91 (2.78-3.04)	0.25
Log10 SVI (mm/BSA)	1.46 (1.32-1.59)	1.42 (1.29-1.55)	0.13	1.59 (1.56-1.62)	1.58 (1.55-1.61)	0.85	1.69 (1.59-1.80)	1.69 (1.59-1.80)	0.91
Log10 CI (mm/BSA)	3.37 (3.22-3.53)	3.31 (3.16-3.45)	**0.01**	3.55 (3.47-3.54)	3.47 (3.44-3.50)	**0.04**	3.62 (3.50-3.74)	3.58 (3.46-3.70)	0.06

BSA, body surface area*; CO*, cardiac output; *CI* cardiac index; *DBP*, diastolic blood pressure; *HR*, heart rate; *MAP*, mean arterial pressure; *SV*, stroke volume; *SVI*, stroke volume index; *SBP*, systolic blood pressure; *TPR*, total peripheral resistance

Within each group there was no significant difference in BP across the trimesters (Table 4.3). When comparing the groups, the post-bariatric surgery women had lower systolic blood pressure (SBP) in all trimesters and lower diastolic blood pressure (DBP) and mean arterial pressure (MAP) in the second trimester compared to the no surgery group. In the overall analysis across all trimesters, the SBP, DBP and MAP were lower in the post-bariatric surgery women compared to the no surgery group (Table 4.4, Figure 4.1).

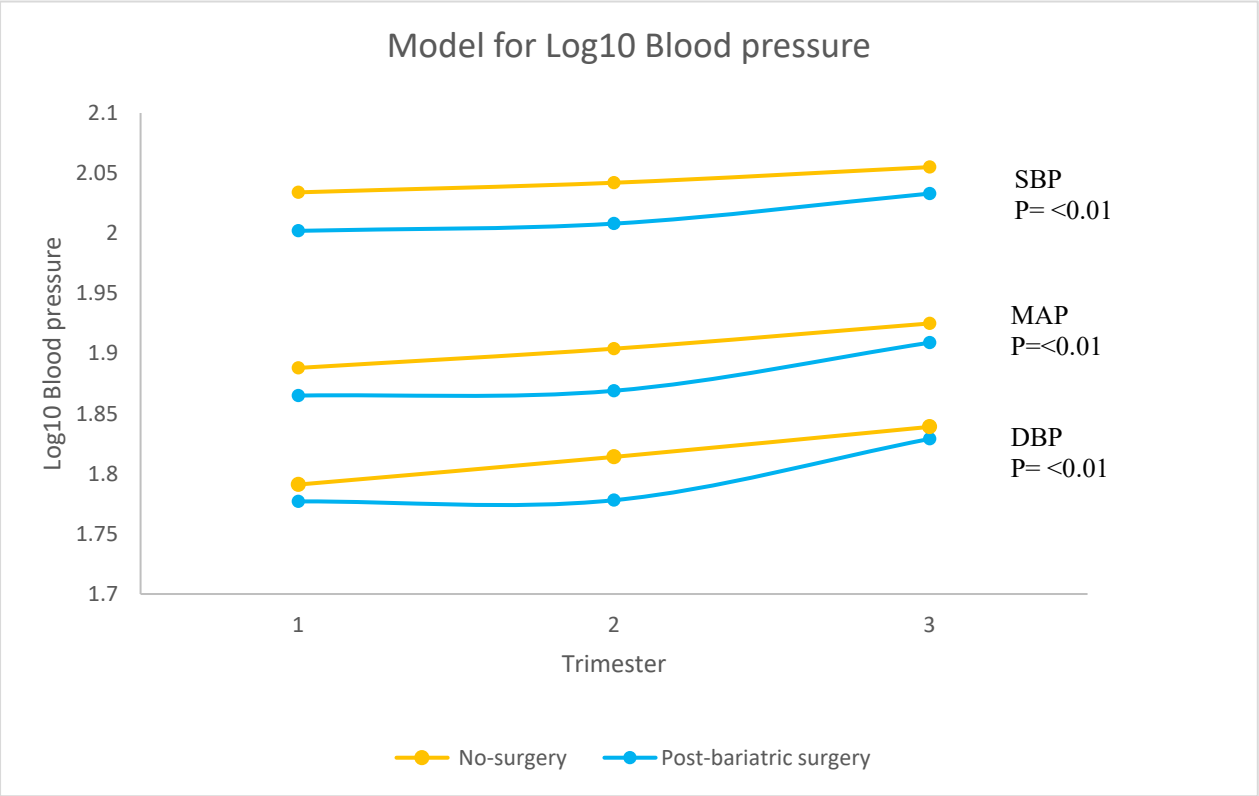


Figure 4.1. Mixed model analysis systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP) across trimesters in both groups.

The HR was significantly higher in the third compared to first trimester in both groups (Table 4.3). When comparing the groups, the HR was lower in the post-bariatric group in all trimesters and the overall time analysis compared to the no surgery group (Table 4.4, Table 4.5, Figure 4.2).

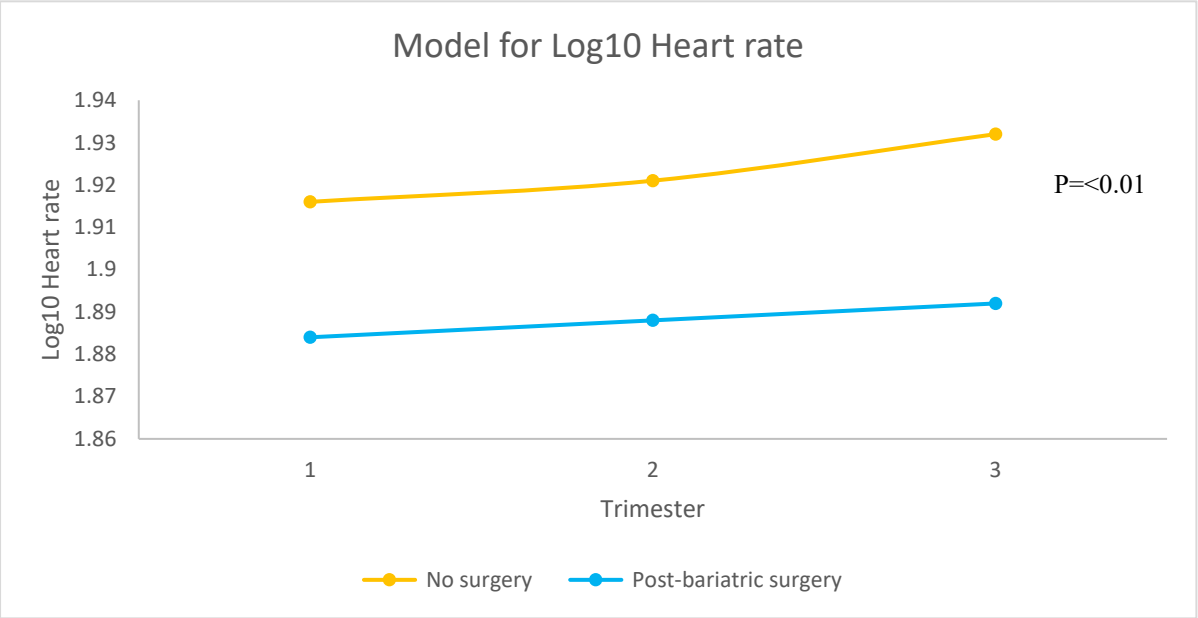


Figure 4.2 Mixed model analysis for heart rate across trimesters in both groups

The SV trended upwards across trimesters in both groups however there was no significant difference between trimesters within groups or between the groups (Table 4.3 and 4.4 respectively). The CO and CI trended upwards across trimesters in both groups and was significantly higher in the third compared to first trimester (Table 4.3). In addition, there was a significant increase between the first and second trimester in the post-bariatric surgery group. When comparing the groups, the CO was lower in the post-bariatric surgery women compared to the no surgery group in all trimesters and the overall analysis (Table 4.4, Table 4.5, Figure 4.3). The CI was significantly lower in the post-bariatric surgery group in the first and second trimester as well as in the overall analysis (Table 4.4).

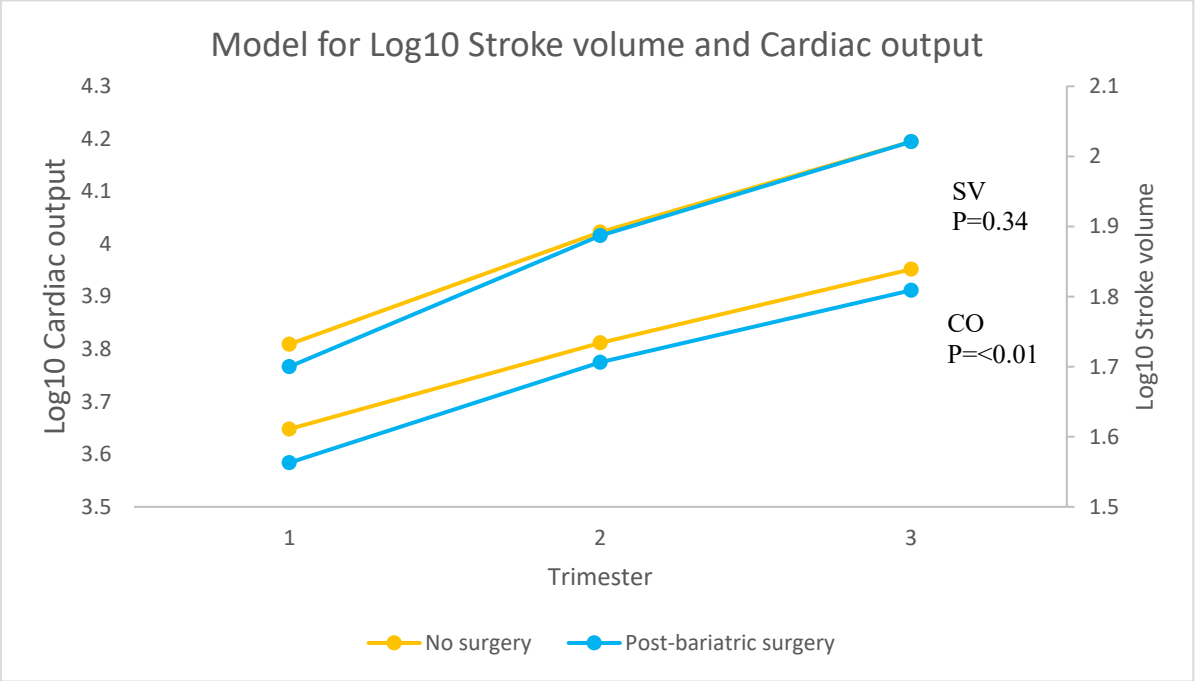


Figure 4.3. Mixed model analysis for stroke volume (SV) and cardiac output (CO across trimesters in both groups

The TPR trended downwards across trimesters in both groups and was significantly lower in the third compared to first trimester (Table 4.3); in addition, there was a significant decrease between the first and second trimester in the post-bariatric surgery group. When comparing the groups, there was no significant difference in TPR (Table 4.4, Figure 4.4).

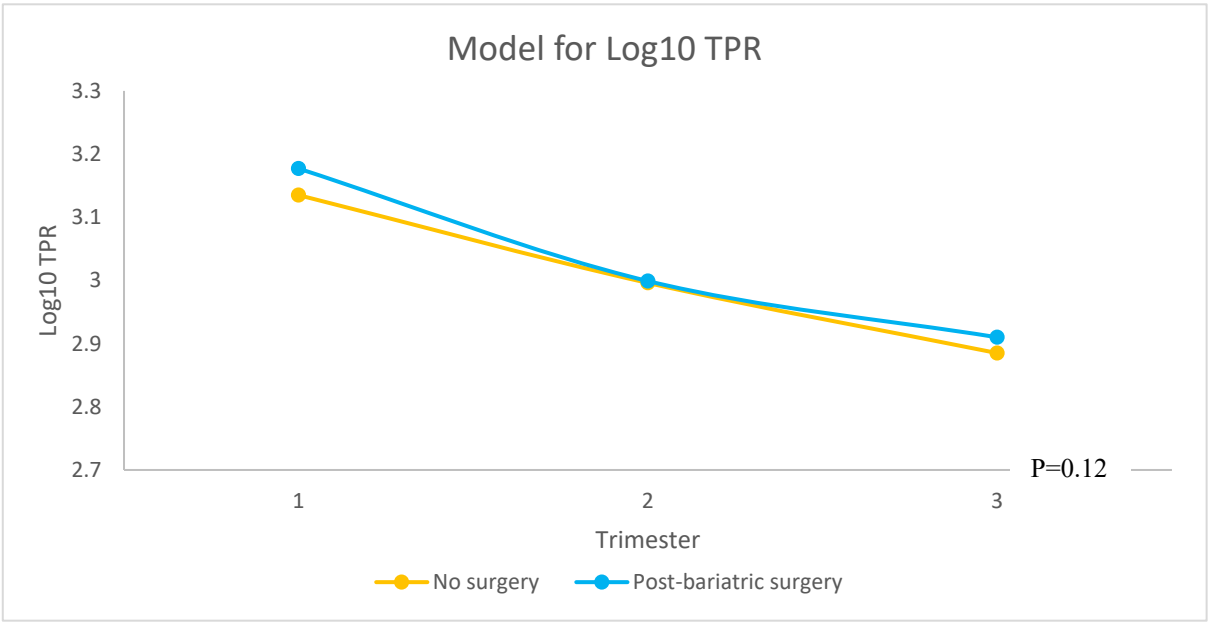


Figure 4.4. Mixed model analysis for total peripheral resistance (TPR) across trimesters in both groups

Cardiac geometry

The median raw values of the haemodynamic variables in the three trimesters of pregnancy and comparisons between the groups are given in Table 4.6. Within each group the trimesters were compared and for significant differences, the mean difference and p values for trimester 1 vs 2, trimester 1 vs 3 and trimester 2 vs 3 are given in Table 4.7.

Table 4.6. Cardiac geometry, median (interquartile range) for each trimester and group with p values of group comparison

	1st Trimester			2nd Trimester			3rd Trimester		
	No-surgery N=26	**Post-bariatric surgery N=26**	**P**	**No-surgery N=41**	**Post-bariatric surgery N=41**	**P**	**No-surgery N=36**	**Post-bariatric surgery N=36**	**P**
LA (mm)	39 (36.8-41)	37.5 (35-41)	0.47	41 (37-42)	40 (38-42.5)	0.97	40 (36.3-42)	40 (37-41.5)	0.87
LA index (mm/BSA)	19 (18-21.1)	19.3 (17.1-20.6)	0.83	19.8 (18.3-21.4)	19.8 (17.7-22.3)	0.92	19.6 (17.4-21)	19.7 (17.5-21.5)	0.37
Aorta (mm)	27 (25-29)	27 (25-28)	0.30	27 (26-29)	27 (26-28)	0.81	28 (25-29.8)	27 (26-29)	0.75
Ascending aorta (mm)	28 (26.8-30.3)	28 (27-29)	0.90	28 (26-30)	28 (26-29)	0.83	28 (26-30)	28 (27-29)	0.54
LVOT (mm)	20 (19-21.3)	20 (20-21)	0.98	21 (20-22)	21 (20-22)	0.82	20.5 (20-22)	21 (20-22)	0.27
IVS (mm)	8 (7-9)	8 (7-9)	0.56	8 (8-9)	8 (7.5-9)	0.77	9 (8-10)	8.5 (7.3-10)	0.48
LVEDD (mm)	48 (45.8-51.3)	48.5 (46.8-51.3)	0.71	50 (47-55.8)	50 (48-52)	0.73	52 (47-54)	51 (48.3-54.8)	0.83
LVEDD index (mm/BSA)	23.2 (21.7-27.1)	24.8 (21.9-26)	0.81	25.2 (23.1-26.6)	24.6 (22.6-26.6)	0.63	25.6 (23-27.1)	25.4 (23.4-27.3)	0.62
PW (mm)	9 (7-9.3)	8.5 (8-9)	0.92	9 (8-10)	9 (8-10)	0.46	10 (8-11)	9 (8-10)	0.15

RWT	0.37 (0.33-0.43)	0.36 (0.33-0.41)	0.94	0.39 (0.35-0.43)	0.38 (0.34-0.41)	0.93	0.41 (0.35-0.44)	0.4 (0.36-0.41)	0.12
LVM (g)	142.8 (121-165.9)	138.2 (120.2-159)	0.99	162.3 (131.1-178.5)	155.1 (134.7-175.9)	0.42	173.5 (140.6-218.5)	165 (139.8-198)	0.38
LVM index (g/BSA)	68.5 (63-79.3)	70.8 (61.2-77.8)	0.88	80.4 (68.4-89.3)	75.4 (67.4-85.8)	0.51	82.8 (70.5-101.1)	83 (71.3-92.2)	0.68

BSA, body surface area*; IVS*, interventricular septum; *LA*, left atrium diameter; *LVEDD*, left ventricle end-diastolic diameter; *LVM*, left ventricular mass; *LVOT*, left ventricle outflow tract; *PW*, posterior wall thickness; *RWT*, relative wall thickness; *BSA*, body surface area

Table 4.7. Mean difference in cardiac geometry between trimesters in the two groups of women (actual values given in Table 4.6). All comparisons have been adjusted by the Bonferroni correction for multiple tests. (T1: 11-14 weeks, T2: 20-24 weeks, T3: 30-32 weeks)

No-surgery, N=22						
	T 1 vs 2		T 1 vs 3		T 2 vs 3	
	Mean difference	P	Mean difference	P	Mean difference	P
LVEDD (mm)	0.7 (2.5)	0.53	1.4 (5.2)	0.77	0.3 (4.5)	0.8
LVEDD index (mm/BSA)	0.4 (1.2)	0.43	0.2 (2.7)	0.6	0.2 (2.3)	0.9
LVM (g)	13.6 (23.5)	0.14	21 (36)	**0.02**	7.5 (21.1)	0.62
LVM index (g/BSA)	6.8 (11.3)	0.11	10.3 (17.9)	**0.03**	6.7 (18.7)	0.64
Post-bariatric surgery, N=22						
	T 1 vs 2		T 1 vs 3		T 2 vs 3	
	Mean difference	P	Mean difference	P	Mean difference	P
LVEDD (mm)	1.7 (2.3)	0.07	3.6 (4.1)	**0.01**	1.9 (4.4)	0.19
LVEDD index (mm/BSA)	0.9 (1.2)	0.41	1.7 (1.9)	**<0.05**	0.8 (2.1)	0.33
LVM (g)	14.3 (12.2)	0.06	32.7 (35.7)	**0.01**	18.5 (36.5)	0.08
LVM index (g/BSA)	7.2 (6.2)	0.05	15.7 (16.3)	**<0.001**	8.4 (17.3)	0.07

BSA, body surface area; *LVEDD*, left ventricle end-diastolic diameter; *LVM*, left ventricular mass

The left ventricle end-diastolic diameter (LVEDD) trended upwards across trimesters in both groups with a significant increase in the third compared to first trimester in the post-bariatric surgery group (Table 4.7). When comparing the groups there was no significant difference. For both groups, the LA (left atrium) diameter, intraventricular septum (IVS), posterior wall (PW) and relative wall thickness (RWT) showed a slight trend upwards across trimesters, however, there was no significant differences between trimesters or between the groups (Table 4.7). The LV mass significantly increased from the first compared to third trimester in both groups however, there was no difference between the groups (Table 4.7).

Systolic, diastolic and longitudinal function

The mean/median raw values of the systolic, diastolic and longitudinal function variables in the three trimesters of pregnancy and comparisons between the groups are given in Table 4.8. Within each group the trimesters were compared and for significant differences, the mean difference and p values for trimester 1 vs 2, trimester 1 vs 3 and trimester 2 vs 3 are given in Table 4.9.

Table 4.8. Systolic, diastolic and longitudinal function, median (interquartile range)/mean (standard deviation) for each time point and group with p values.

	1st Trimester			**2nd Trimester**			**3rd Trimester**		
	No-surgery N=26	**Post-bariatric surgery N=26**	**P**	**No-surgery N=41**	**Post-bariatric surgery N=41**	**P**	**No-surgery N=36**	**Post-bariatric surgery N=36**	**P**
Systolic function									
EDV (mm)	99.5 (76.3-116.5)	91.5 (75.8-103.3)	0.12	101 (84.5-112)	95 (85-113)	0.85	105 (81-112)	95 (88-111.8)	0.50
EDV index (mm/BSA)	47.4 (39.7-53.9)	43.5 (38.7-51.3)	0.21	47.9 (43.1-52.4)	48.5 (42.6-53.7)	0.76	49 (39.1-54.2)	49.1 (43.8-54.8)	0.31
ESV (mm)	37 (33.8-45.3)	33 (29.8-38.5)	**0.03**	40 (33-48)	38 (32-44)	0.55	39 (32-46)	40 (32.5-45)	0.63
ESV index (mm/BSA)	18.9 (17-20.7)	17 (14-18.8)	**0.03**	19.2 (15.6-23.3)	19.2 (16.5-22.8)	0.97	19.2 (15.4-21.1)	19.3 (16.3-22.9)	0.54
EF (%)	59.5 (55-63.3)	61.5 (57-63.5)	0.18	60 (54-64)	62 (56.5-64)	0.27	59 (57-62)	59.5 (55-64.8)	0.94
TDI s' (cm)	13 (11.5-14)	12 (11-14)	0.51	13 (12-15)	13 (11.8-15)	0.89	13 (12-15)	12 (10.8-14)	0.022
Diastolic function									
E velocity (m/s)	84.5 (13.8)	85.0 (7.7)	0.85	79.1 (15.4)	86.7 (16.3)	**0.04**	75.9 (18.8)	77.65 (15.17)	0.66
A velocity (m/s)	57.1 (10.3)	54.0 (9.2)	0.27	58.9 (11.2)	56.1 (10.9)	0.25	62.4 (13)	55.73 (10)	**0.02**

E/A ratio	1.5 (0.25)	1.6 (0.3)	0.15	1.4 (0.3)	1.5 (0.3)	**0.01**	1.2 (0.3)	1.42* (0.3)	**0.02**
E' lateral (m/s)	14.8 (2.4)	16.1 (3.1)	0.10	13.5 (3.1)	15.9 (4.6)	**0.01**	13.2 (2.7)	13.5 (3)	0.69
E' medial (m/s)	10.5 (1.9)	11.1 (2.8)	0.36	10 (2.4)	10.9 (2.4)	0.08	9.4 (1.8)	9.97 (2.6)	0.28
E/ E' ratio	6.8 (1.1)	6.5 (1.3)	0.45	6.8 (1.4)	6.7 (1.5)	0.74	6.8 (2.1)	6.82 (1.8)	1.00
LAV (ml)	57.3 (12.1)	56.0 (7.8)	0.67	62.4 (9.5)	58.3 (9.1)	0.06	63.2 (13.7)	59.6 (8)	0.18
LAV index (ml/BSA)	28.2 (4.7)	28.1 (3.)	0.92	30.4 (3.9)	29.0 (5.0)	0.18	31.1 (6.3)	29.9 (5.3)	0.40
Longitudinal function									
TAPSE (mm)	22.5 (21-25.3)	22.5 (19-24.3)	0.51	23.5 (21-27)	22.5 (21-25.8)	0.36	23 (21-25.3)	21(19-25)	0.12
MAPSE septal (mm)	16 (14.5-17)	14 (13-17)	0.13	14 (13-16)	14(13-15)	0.94	13 (12-16)	13(12-15)	0.73
MAPSE lateral (mm)	18 (15-19)	17 (15.3-20)	0.72	15 (13-17)	16 (15-18.8)	0.05	15 (13-17)	16 (14-17.5)	0.20

BSA, body surface area*; E/A ratio*, mitral inflow E-wave/A-wave filling; *E' lateral*, tissue Doppler imaging E prime measured at lateral mitral annulus; *E' medial*, tissue Doppler imaging E prime measured at medial mitral annulus; *E/E' ratio*, E-wave mitral inflow/ mean E' lateral and E' medial; *EF*, ejection fraction; *EDV*, end-diastolic volume; *LAV*, left atrial volume; *ESV*, end-systolic volume; *TDI s'*, tissue Doppler imaging s' at the lateral tricuspid annulus; *MAPSE*, mitral annular plane systolic excursion; TAPSE, tricuspid annular plane systolic excursion

Table 4.9. Mean difference in systolic, diastolic and longitudinal function between trimesters in the two groups of women (actual values given in Table 4.8). All comparisons have been adjusted by the Bonferroni correction for multiple tests. (T1: 11-14 weeks, T2: 20-24 weeks, T3: 30-32 weeks)

No-surgery, N=22						
	T 1 vs 2		T 1 vs 3		T 2 vs 3	
	Mean difference	P	Mean difference	P	Mean difference	P
Systolic function						
EDV index (mm/BSA)	0.6 (12.6)	0.96	-0.5 (13.3)	0.85	-1 (7.9)	0.78
ESV (mm)	0.9 (10.9)	0.7	-0.3 (11.7)	0.8	-1.1 (8.7)	0.57
ESV index (mm/BSA)	0.5 (5.5)	0.67	0 (5.9)	0.81	-0.5 (4.6)	0.72
Diastolic function						
E/A ratio	-0.1 (0.3)	0.06	-0.2 (0.3)	**0.01**	-0.1 (0.4)	0.23
LAV index (ml/BSA)	4.2 (7.5)	0.14	5.7 (9)	**0.02**	1.5 (6.7)	0.05
Longitudinal function						
MAPSE septal (mm)	-1.8 (2.6)	**0.03**	-2.4 (3.8)	**0.02**	-0.6 (2.2)	0.36
MAPSE lateral (mm)	-2.5 (3.2)	**0.02**	-2.3 (3.8)	**0.02**	0.2 (2.8)	0.88
Post-bariatric surgery, N=22						
	T 1 vs 2		T 1 vs 3		T 2 vs 3	
	Mean difference	P	Mean difference	P	Mean difference	P
Systolic function						
EDV index (mm/BSA)	5.8 (9.2)	0.03	6.3 (9.8)	**0.02**	0.5 (5.6)	0.89
ESV (mm)	7.4 (11.7)	0.01	7 (11.7)	**0.03**	-0.4 (7.8)	0.52
ESV index (mm/BSA)	3.4 (5.4)	0.01	3.2 (5.6)	**0.03**	-0.3 (3.9)	0.56
Diastolic function						
E/A ratio	-0.1 (0.3)	0.34	-0.2 (0.3)	**0.04**	-0.1 (0.2)	0.15
LAV index (ml/BSA)	-1 (7.6)	1	1.1 (9.5)	0.43	2.1 (11.1)	0.47
Longitudinal function						
MAPSE septal (mm)	-0.9 (3.8)	0.86	-1.4 (3.1)	0.06	-0.5 (3.9)	0.06
MAPSE lateral (mm)	0.3 (3.2)	0.82	-1.4 (3.2)	0.12	-1.7 (2.4)	0.11

BSA, body surface area*; E/A ratio*, mitral inflow E-wave/A-wave filling; *EDV*, end-diastolic volume; *LAV*, left atrial volume; *ESV*, end-systolic volume; *TDI s'*, tissue Doppler imaging s' at the lateral tricuspid annulus; *MAPSE*, mitral annular plane systolic excursion

Mixed model analysis was used to compare the diastolic function between groups at each trimester and overall, after adjustment for age, race, BMI, gestational age, smoking and GDM. The overall group comparison across all trimesters is given in Table 4.10 and the estimated marginal means at each trimester for each group is given in Table 4.11.

Table 4.10. Multilevel linear mixed-effects models for diastolic function, overall group comparison across all trimesters.

Overall group comparisons (All trimesters)		
	Mean Difference No-surgery – Post-bariatric surgery (95% Confidence Interval for Difference)	P
E/A ratio	-0.158 (-0.239-(-0.076))	**<0.001**
E' lateral (m/s)	-1.364 (-2.234-(-0.493))	**<0.01**
E' medial (m/s)	-0.713 (-1.364-(-0.061))	**0.03**
E/ E' ratio	0.151 (-0.269-(0.57))	0.48
LAV (ml)	2.686 (0.007-5.365)	**<0.05**
LAV index (ml/BSA)	0.88 (-0.479-(2.24))	0.20

BSA, body surface area*; E/A ratio*, mitral inflow E-wave/A-wave filling; *E' lateral*, tissue Doppler imaging E prime measured at lateral mitral annulus; *E' medial*, tissue Doppler imaging E prime measured at medial mitral annulus; *E/E' ratio*, E-wave mitral inflow/ mean E' lateral and E' medial; *LAV*, left atrial volume

Table 4.11. Multilevel linear mixed-effects models for diastolic function. Estimated marginal means (95% CI) for each trimester and group are given.

	1st Trimester			**2nd Trimester**			**3rd Trimester**		
	No-surgery N=26	**Post-bariatric surgery N=26**	**P**	**No-surgery N=41**	**Post-bariatric surgery N=41**	**P**	**No-surgery N=36**	**Post-bariatric surgery N=36**	**P**
E/A ratio	1.5 (1.37-1.64)	1.61 (1.46-1.75)	0.17	1.37 (1.24-1.51)	1.56 (1.43-1.70)	**<0.01**	1.26 (1.11-1.40)	1.4 (1.26-1.55)	**0.02**
E' lateral (m/s)	15 (13.6-16.3)	16.3 (15-17.7)	0.08	13.6 (12.1-15.2)	16.1 (14.6-17.6)	0.01	13.4 (12.1-14.8)	13.7 (12.4-15)	0.64
E' medial (m/s)	10.4 (9.3-11.6)	11.1 (10-12.2)	0.29	9.9 (8.9-10.8)	10.8 (9.8-11.8)	0.06	9.3 (8.3-10.3)	9.9 (8.9-10.9)	0.35
E/ E' ratio	6.7 (6.08-7.32)	6.4 (5.77-7.03)	0.38	6.81 (6.19-7.42)	6.66 (6.06-7.25)	0.61	6.77 (6-7.54)	6.77 6.01-7.53)	0.93
LAV (ml)	58.8 (53.5-62.5)	57.4 (52.7-62)	0.86	63.1 (59-67.2)	59.3 (55.1-63.5)	0.06	63.7 (58.8-68.5)	60.8 (55.8-65.7)	**0.02**
LAV index (ml/BSA)	28.4 (26.1-30.7)	28.44 (26.08-30.79)	1	30.7 (28.7-32.7)	29.5 (27.4-31.6)	0.24	31.2 (28.9-33.6)	30.2 (27.7-32.7)	0.25

BSA, body surface area*; E/A ratio*, mitral inflow E-wave/A-wave filling; *E' lateral*, tissue Doppler imaging E prime measured at lateral mitral annulus; *E' medial*, tissue Doppler imaging E prime measured at medial mitral annulus; *E/E' ratio*, E-wave mitral inflow/ mean E' lateral and E' medial; *LAV*, left atrial volume

Within both groups the end-diastolic volume (EDV) and end-systolic volume (ESV) showed a slight upward trend across trimesters with a significant increase in EDV index and ESV index between the first and third trimester in the post-bariatric surgery group (Table 4.9). When comparing the groups, in the first trimester the ESV index was significantly lower in the post-bariatric group compared to the no surgery group however there was no difference in the other trimesters. There was no difference between trimesters or groups for ejection fraction (EF) or TDI s' at the right lateral annulus.

Within both groups the E/A ratio decreased through the trimesters and was significantly lower in the third compared to first trimester (Table 4.9). When comparing the groups, the E/A ratio was significantly higher in the post-bariatric group compared to the no surgery group in the second and third trimester as well as in the overall analysis (Table 4.10, Figure 4.5).

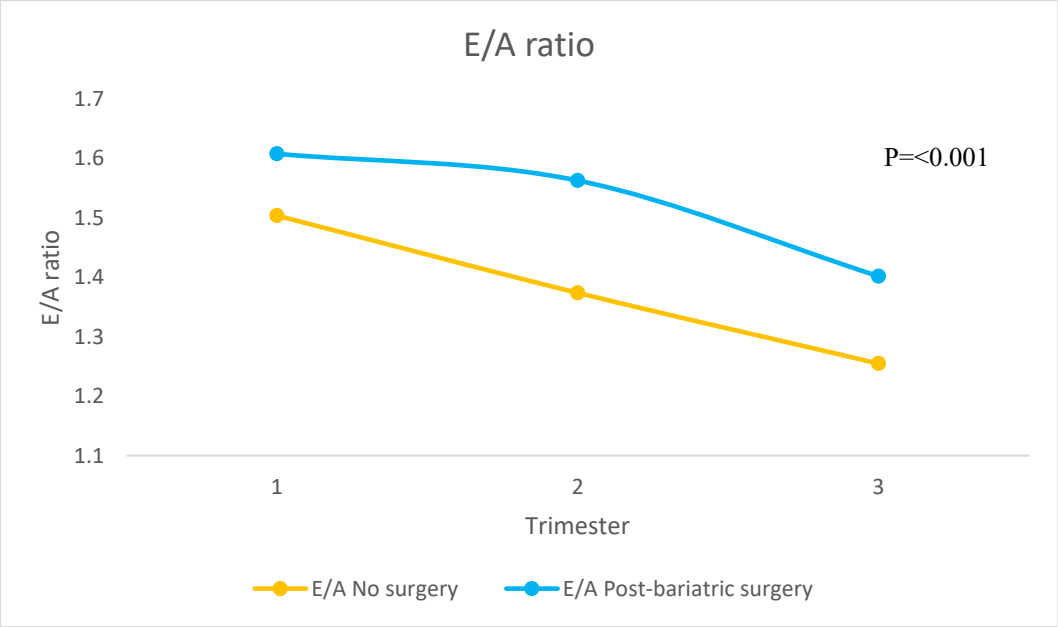


Figure 4.5. Mixed model analysis for mitral inflow E-wave/A-wave (E/A) ratio across trimesters in both groups examined.

E' lateral and E' medial trended downwards across trimesters in both groups, however, there was no significant difference (Table 4.9). When comparing the groups at each trimester, there was no significant difference, however in the overall analysis across all trimesters, E' lateral and E' medial were significantly higher in the post-bariatric surgery group compared to the no surgery group (Table 4.10, Figure 4.6). There was no difference between trimesters or groups for the E/E' ratio.

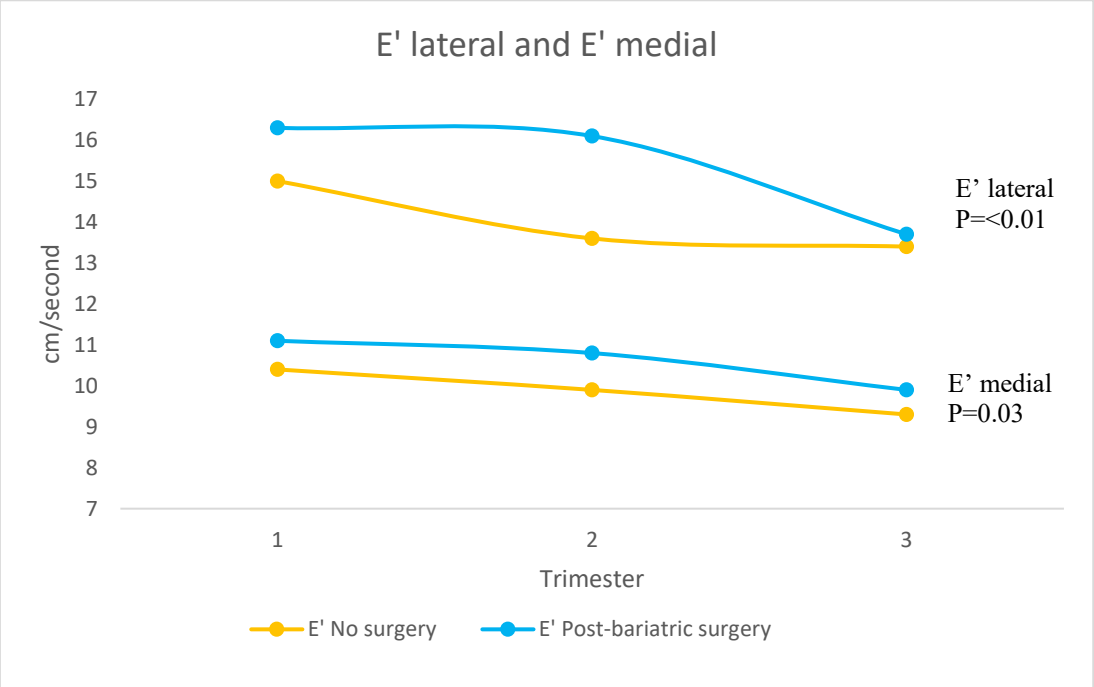


Figure 4.6. Mixed model analysis for Tissue Doppler imaging E' lateral and medial across trimesters in both groups examined.

The left atrial (LA) volume trended upwards through the trimesters in both groups with a significant increase in the third compared to first trimester in the no-surgery group (Table 4.9). When comparing the groups, the LA volume was significantly lower in the post-bariatric surgery group in the overall analysis compared to the no-surgery group (Table 4.11, Figure 4.7) although this did not persist after correction for BSA.

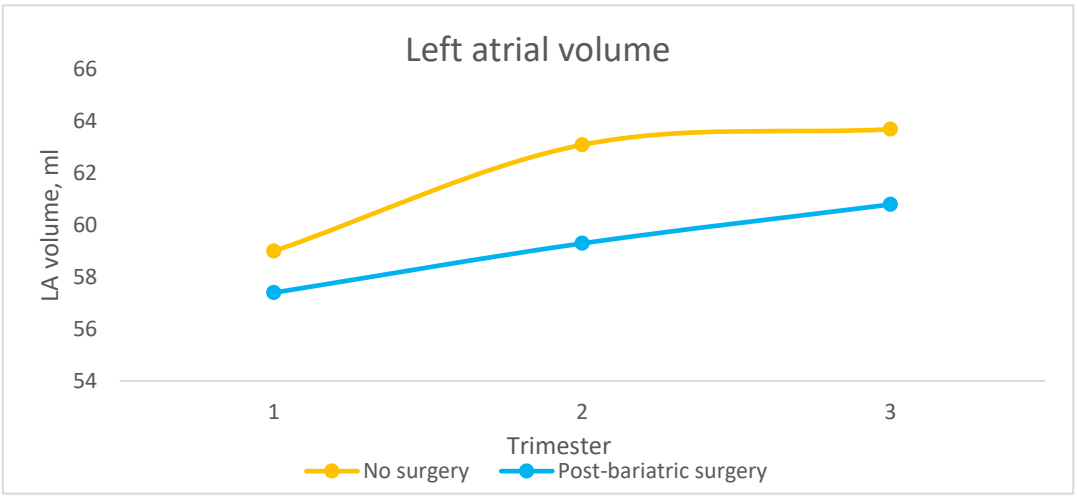


Figure 4.7. Mixed model analysis for left atrial volume across trimesters in both groups examined.

Lateral and septal mitral annular plane systolic excursion (MAPSE) trended downwards across the trimesters and significantly decreased from the first to the second and third

trimester in the no-surgery group. There was no difference between the groups (Table 4.10). There was no difference between trimesters or groups in tricuspid annular plane systolic excursion (TAPSE) (Table 4.10).

Global longitudinal and circumferential strain

A subgroup of 15 women in each group (no-surgery and post-bariatric) with adequate image quality were used for strain analysis. The mean (standard deviation) in the three trimesters of pregnancy and comparisons between the groups are given in Table 4.12. Within each group, there was no significant difference between the trimesters.

Table 4.12. Global longitudinal strain and global circumferential strain, mean (standard deviation) for each trimester and group with p values of group comparison.

	1st Trimester		
	No-surgery	Post-Bariatric Surgery	P
GLS	-16.2 (2.9)	-18.0 (2.5)	0.07
GCS	-19.2 (4.2)	-21.1 (5.5)	0.48
	2nd Trimester		
	No-surgery	Post bariatric surgery	P
GLS	-16.1 (3.4)	-17.1 (2.9)	0.19
GCS	-20.3 (2.039)	-20.8(3.6)	0.65
	3rd Trimester		
	No-surgery	Post bariatric surgery	P
GLS	-15.3 (2.0)	-17 (3.5)	0.18
GCS	-17.5 (3.8)	-22.1 (3.4)	**0.01**

GCS global circumferential strain; *GLS*, global longitudinal strain

Mixed model analysis was used to compare the GLS and GCS between groups at each trimester and overall, after adjustment for age, race, gestational age, GDM and smoking. The overall comparison is given in Table 4.13 and the estimated marginal means at each trimester with group comparison is given in Table 4.14.

Table 4.13. Multilevel linear mixed-effects models for global longitudinal strain and global circumferential strain, overall group comparison across all trimesters

Overall group comparisons (All trimesters)		
	Mean Difference No-surgery – Post-bariatric surgery (95% Confidence Interval for Difference)	**P**
GLS	1.79 (0.55-3.04)	**<0.01**
GCS	2.35 (0.4-4.27)	**0.02**

GCS global circumferential strain; *GLS*, global longitudinal strain

Table 4.14. Multilevel linear mixed-effects models for global longitudinal strain and global circumferential strain. Estimated marginal means (95% CI) for each trimester and group are given.

	1st Trimester			**2nd Trimester**			**3rd Trimester**		
	No surgery	**Post-Bariatric Surgery**	**P**	**No surgery**	**Post-Bariatric Surgery**	**P**	**No surgery**	**Post-Bariatric Surgery**	**P**
GLS	-17.78 (-17.26-(-12.28))	-18.45 (-19.14-(-13.76))	0.13	-16.68 (-18.31-(-13.05))	-17.91 (-19.97-(-14.66))	0.18	-15.86 (-18.55-(-13.18))	-17.75 (-20.42-(-15.08))	**<0.01**
GCS	-19.08 (-22.68-(-15.5))	-22.48 (-24.56-(-16.40))	0.99	-19.17 (-23.33-(-16.61))	-21.88 (-23.84-(-17.92))	0.32	-17.38 (-20.85-(-13.9))	-20.11 (-25.44-(-18.778))	**0.03**

Within each group we found no significant difference between the trimesters in GLS or GCS. When comparing the groups, we found that the GLS and GCS were lower in the post-bariatric women compared to the no-surgery group in the third trimester and in the overall analysis across all trimesters (Table 4.13).

Birthweight

The birthweight percentiles in both groups examined are given with maternal characteristics in Table 4.1. We then examined whether any of the maternal cardiovascular parameters including MAP, CO and TPR correlate with birthweight (BW) percentile (Table 4.17, Table 4.18 and Figures 4.11-4.13).

Table 4.15. Pearson's correlation (R) of cardiac output, total peripheral resistance and mean arterial pressure with birth weight percentile in each group and trimester with p value

		No surgery		Post-Bariatric surgery	
	Trimester	**R**	**P**	**R**	**P**
CO	1	0.12	0.45	0.18	0.37
	2	0.13	0.41	0.07	0.68
	3	0.20	0.22	0.12	0.47
TPR	1	-0.13	0.44	-0.16	0.42
	2	-0.06	0.71	-0.08	0.60
	3	-0.25	0.12	-0.37	0.83
MAP	1	-0.12	0.45	0.13	0.54
	2	-0.02	0.92	0.05	0.77
	3	-0.17	0.30	0.26	0.12

CO, cardiac output; *MAP*, mean arterial pressure; *TPR*, total peripheral resistance

Table 4.16. Pearson's correlation (R) of cardiac output, total peripheral resistance and mean arterial pressure with birth weight percentile for the whole cohort at each trimester

	Trimester	**R**	**P**
CO	1	0.27	**0.03**
	2	0.18	0.11
	3	0.23	**<0.05**
TPR	1	-0.23	**<0.05**
	2	-0.07	0.56
	3	-0.17	0.14
MAP	1	0.05	0.68
	2	0.16	0.16
	3	0.14	0.23

CO, cardiac output; *MAP*, mean arterial pressure; *TPR*, total peripheral resistance

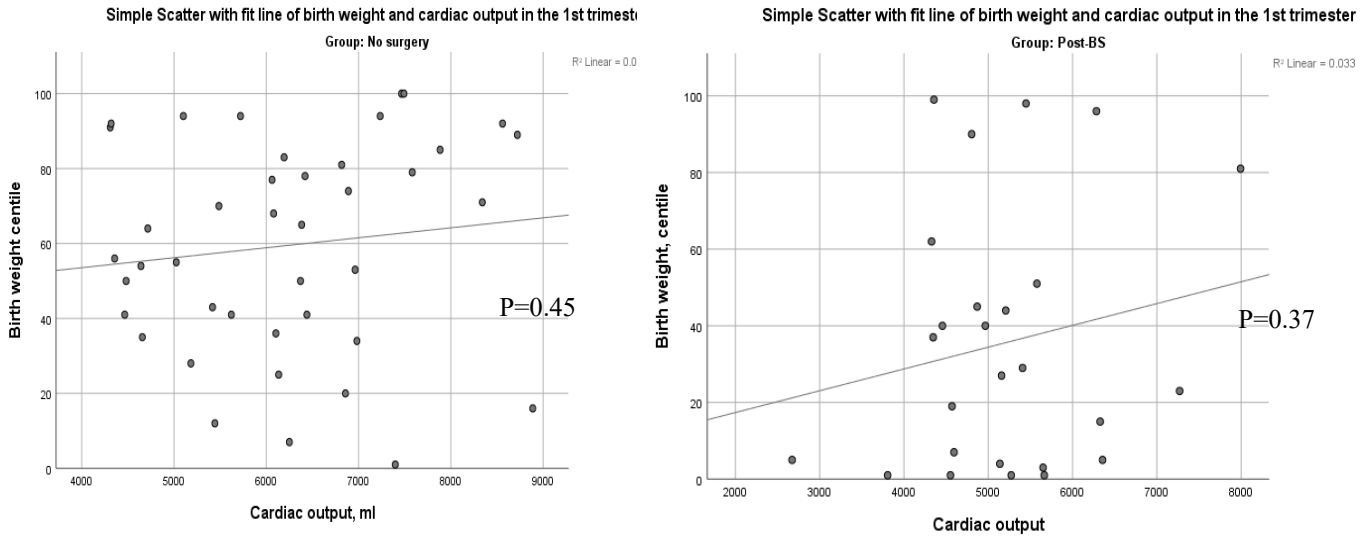
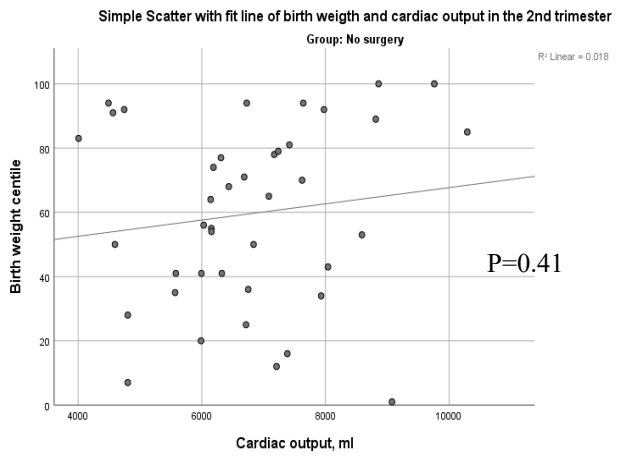


Figure 4.8. Correlation of maternal cardiac output and birth weight percentile in the first trimester in the no-surgery group (left) and post-bariatric surgery group (right)



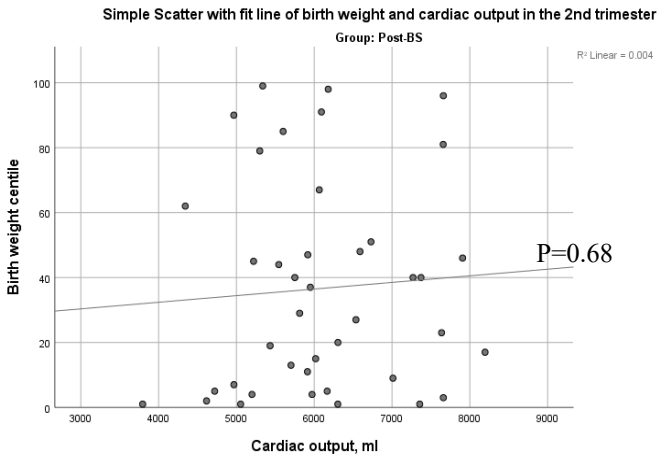
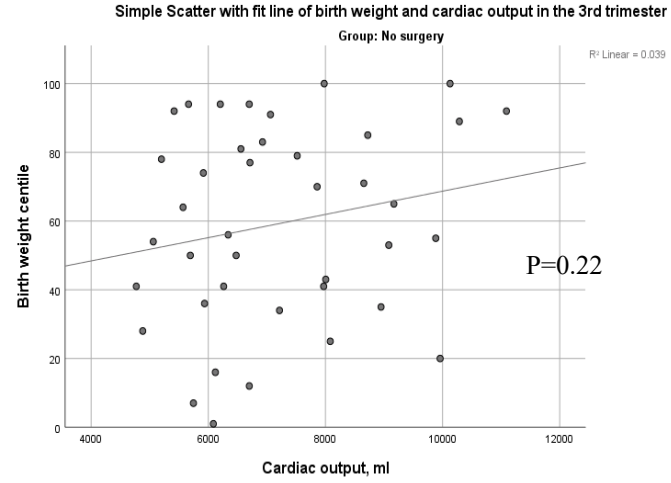


Figure 4 9. Correlation of maternal cardiac output and birth weight percentile in the second trimester in the no-surgery group (left) and post-bariatric surgery group (right)



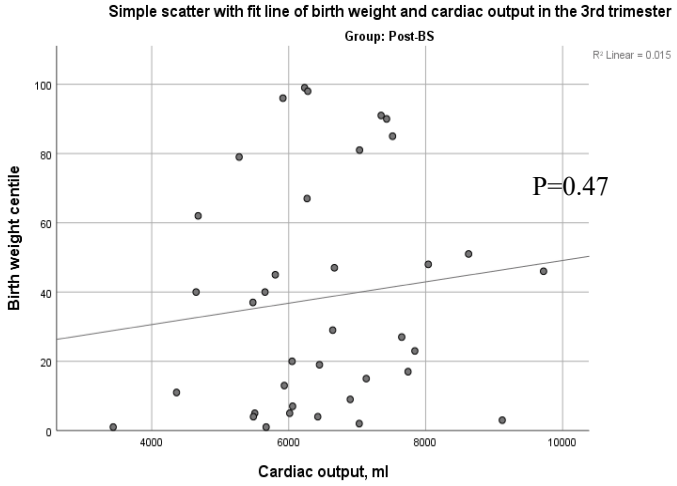
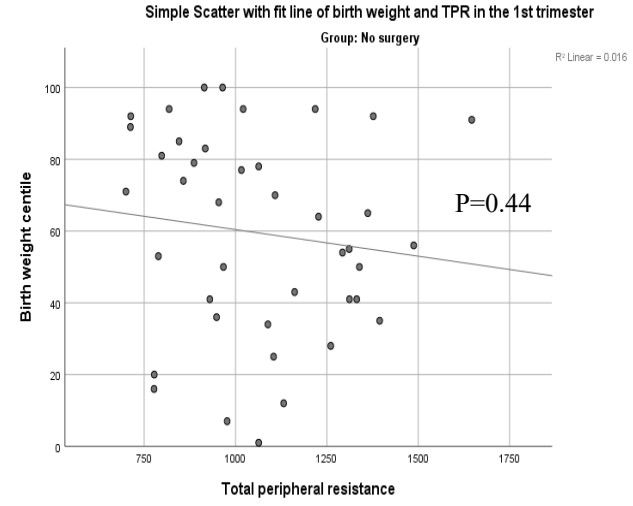


Figure 4.10. Correlation of maternal cardiac output and birth weight percentile in the third



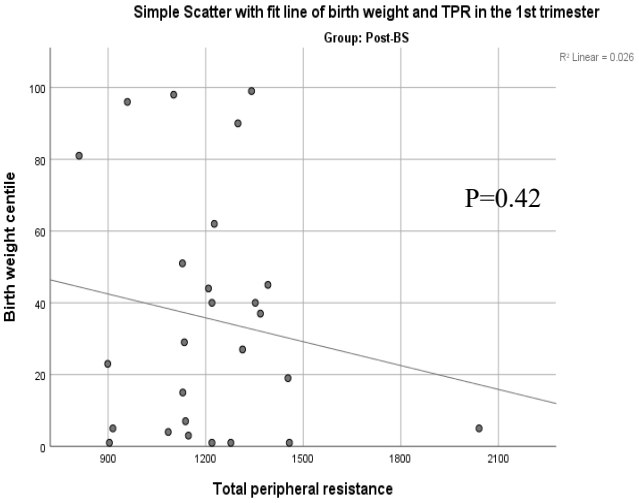


Figure 4.11. Correlation of maternal total peripheral resistance and birth weight percentile in the first trimester in the no-surgery group (left) and post-bariatric surgery group (right)

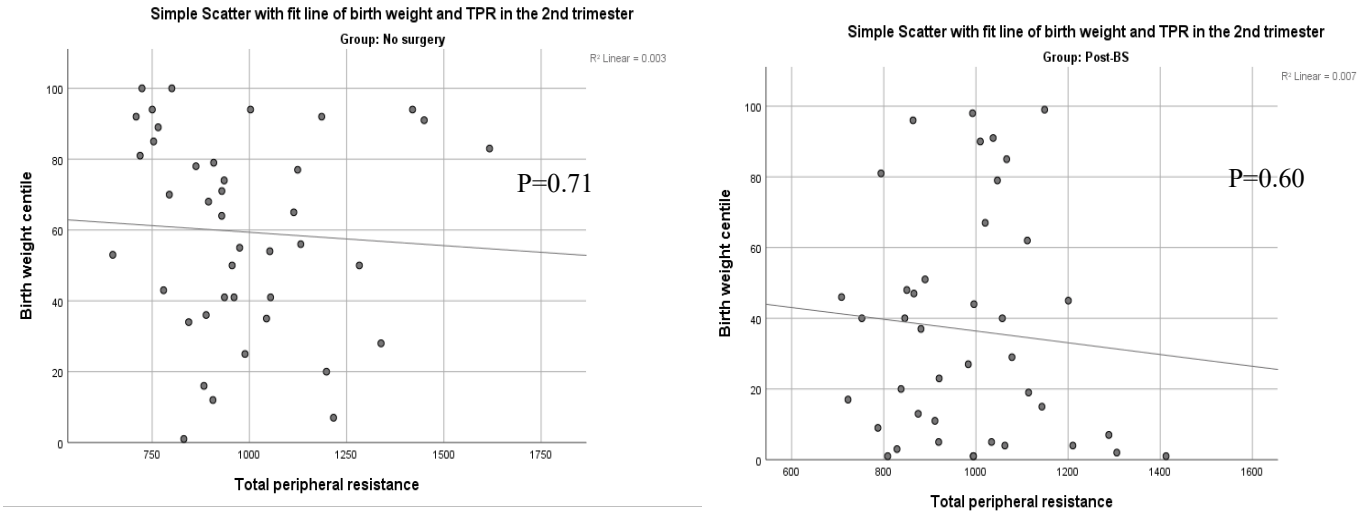


Figure 4.12. Correlation of maternal total peripheral resistance and birth weight percentile in the second trimester in the no-surgery group (left) and post-bariatric surgery group (right)

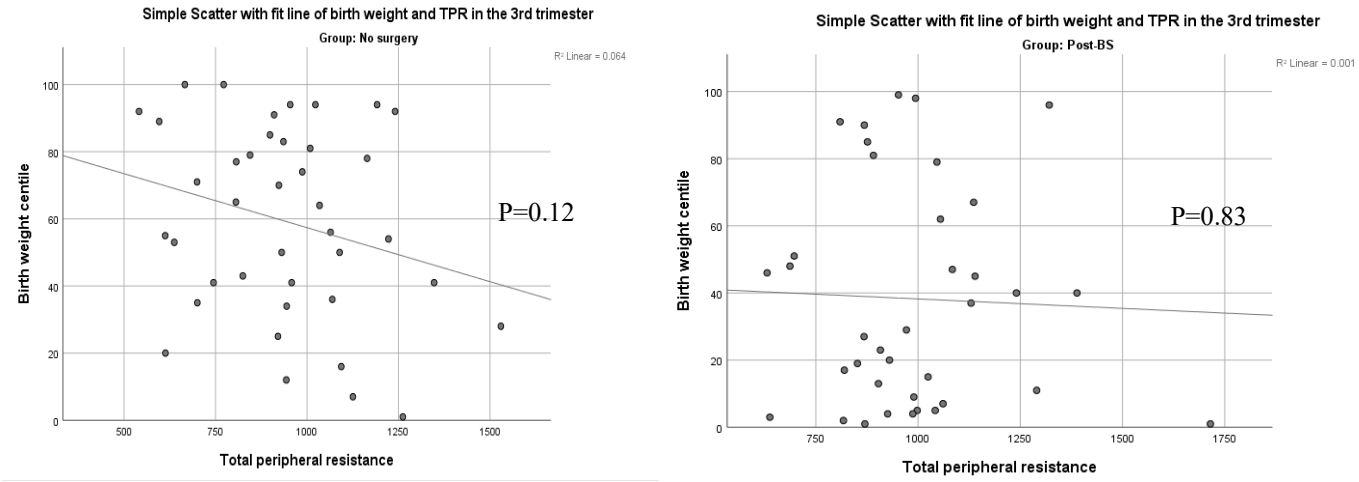


Figure 4.13. Correlation of maternal total peripheral resistance and birth weight percentile in the third trimester in the no-surgery group (left) and post-bariatric surgery group (right)

We did not find any significant correlation between CO, TPR or MAP and BW percentile in either group, however as CO increased, BW percentile also trended up and conversely as TPR increased, in BW trended down. When considering the whole cohort, we found a positive correlation between maternal CO (in the first and third trimesters) and BW percentiles, this may not have been seen in the individual groups due to smaller numbers.

Discussion

The study has shown that pregnant women with previous bariatric surgery have better cardiovascular adaptation to pregnancy compared to women with similar early pregnancy BMI but no history of weight loss surgery. Haemodynamically, post-bariatric pregnant women demonstrated lower SBP, DBP, HR and CO. Diastolic indices were more favourable in the post-bariatric women and systolic function, assessed by GLS and GCS were both better in women with previous bariatric surgery. These findings suggest that bariatric surgery has a positive impact on maternal cardiovascular adaptation, which appears to be beyond to what would be expected by weight loss as our groups were closely matched for BMI.

Blood pressure was lower in the post-bariatric surgery group compared to the no surgery group in the overall analysis across trimesters. The mechanisms of obesity hypertension are complex and involve impaired renal pressure natriuresis due to physical compression of the kidneys and activation of the renin angiotensin-aldosterone system (RAAS) and sympathetic nervous system (SNS). Activation of the RAAS is in part due to renal compression as well as SNS activity. The mechanism of SNS activation is not fully understood but thought to involve leptin and the brain melanocortin system as well as hyperinsulinaemia. (8-10) Many studies have found a reduction or resolution in hypertension after bariatric surgery usually due to a combined effect of weight loss and changes in gastrointestinal peptides. (10) It has been reported that BP is lowered as early as one week post-surgery, this is before any meaningful weight loss has occurred and indicates an influence from the surgery itself. (89, 90, 174) It is thought this is due to an early reduction in SNS activity, studies of the SNS after gastric bypass found that there was decrease in sympathetic activity and improvement in the baroreceptor modulation of HR and sympathetic activity. (160, 175) It is suggested that baroreflex impairment is a possible cause of the obesity-related sympathetic activation. (160, 176) Improvement in insulin sensitivity and reduction in leptin after bariatric surgery may also be involved as both lead to direct stimulation of the SNS. (10, 177-179) Furthermore, it has been shown that hyperleptinaemia and hyperinsulinaemia may be regulators of arterial pressure independent of BMI or body fat percentage. (180) Increased plasma concentrations of GLP-1 immediately after gastric bypass is known to improve insulin resistance and may have a natriuretic and diuretic effect. (89, 97, 98, 181, 182) Our findings are in pregnant women who were matched for early pregnancy BMI and therefore are focused on the effects

of bariatric surgery rather than the impact of weight loss alone. We found a lower BP in the post-bariatric group which may suggest the influence of gut hormone manipulation resulting in a reduction in SNS activity. (10, 153, 183) Studies of pregnancy after bariatric surgery report lower rates of PE compared to women with similar pre-surgery or early pregnancy BMI, but no history of weight loss surgery. (111, 117, 118, 155, 184) Further to this, a study of pregnancy after bariatric surgery concluded that the prevalence of hypertensive disorders was consistent with general community levels rather than outcomes from severely obese women. (113) Our findings of lower BP after bariatric surgery may contribute to the mechanism leading to lower rates of PE after bariatric surgery.

The maternal HR increased with gestation in both groups however was lower in the post-bariatric compared to the no-surgery group. In studies outside of pregnancy it has been reported that after bariatric surgery, HR is lower and HR recovery after exercise is improved likely due to reduced sympathetic activity and better parasympathetic modulation. (157-159, 175) Maternal CO and CI increased with gestation in keeping with a physiological increases in SV and HR due to an reduction in resistance leading to vasodilation and volume expansion. (28) Studies of haemodynamic parameters after bariatric surgery outside pregnancy describe a decrease in SV and CO after surgery. (102, 161) It has been shown that SV and CO are related to BSA and it is likely the reduction after bariatric surgery is influenced by the effect of weight loss on the circulating volume. (185, 186) However, a study six weeks after gastric bypass found a reduction in CO and HR that was associated with an increase in baroreceptor sensitivity and independent of changes in body weight, suggesting a shift towards increased parasympathetic control. (88) In our study the changes in maternal HR and SV in the post-bariatric women resulted in a reduction in CO, compared to women without surgery. Of interest, the CO values in the post-bariatric group were similar to the values reported in the literature for women of normal BMI. (72, 162-164) Our groups were closely matched for BMI suggesting that the difference was due to the surgery itself rather than weight loss. Cardiac output plays a pivotal role in the cardiovascular adaptation to pregnancy and has been associated with the development of hypertensive disease in pregnancy. A hyperdynamic circulation with high CO has been reported in the pre-clinical and clinical phase of PE.(56, 173) Considering the lower prevalence of PE following bariatric surgery (111), it can be postulated that the mechanism behind this involves changes in maternal CO post-bariatric surgery.

We confirmed a downward trend of TPR in both groups; consistent with findings in normal pregnancy but we found no difference between the groups. (28)

As far as the maternal cardiac geometry is concerned, we found left ventricular mass increased from the first to third trimester in both groups, in keeping with physiological changes in pregnancy needed to cope with increased preload. (33) There was no differences in the cardiac geometric indices between the groups. Many studies outside the setting of pregnancy describe changes in cardiac geometry after surgery but most of these studies assessed the same individuals before and after surgery and therefore their findings were affected by the weight loss itself. In agreement with this, decrease in LV mass has been shown to be linear to BMI reduction. (103, 187) However, it is also reported that LV mass also correlates with leptin levels indicating the additional cardiovascular effects of gut hormone changes after bariatric surgery.(188, 189)

There was evidence of diastolic improvement in the post-bariatric compared to the no-surgery group. Mothers with previous bariatric surgery had higher E/A ratio, TDI E' lateral/E' medial and lower LA volume compared to the no surgery group. Studies before and after bariatric surgery, outside the setting of pregnancy, conclude that the changes in diastolic function are likely due to an improvement in diastolic dysfunction associated with obesity and that the left atrial volume reflects chronic exposure to increased LV filling pressure. (91) In both groups the E/A ratio deceased with gestation which is in keeping with literature, interestingly, we found that the E/A ratio in the post-bariatric group was approaching that of a normal BMI pregnant population. (33, 39) Outside of pregnancy, LV elastic recoil and myocardial relaxation is swift so most LV filling occurs passively in early diastole with a small amount of filling due to atrial contraction. During pregnancy there is a greater emphasis on atrial contraction resulting in a reduced E/A ratio. This is due to left atrial pressure and, or left ventricle end diastolic pressure increase in the second and third trimester requiring increased atrial contractile force. Another potential mechanism is the increased LV mass in pregnancy which may reduce compliance. (190) As our populations were matched for BMI, it is possible that the surgery itself via the entero-cardiac axis is responsible for improvements in diastolic function. GLP-1 has been shown to improve diastolic function and heart failure survival in animal studies. (191) Levels of GLP-1, have been shown to increase after gastric bypass and positively correlate with diastolic function. (181, 192) Treatment of diabetic patients with GLP-1 showed an improved E/A ratio suggesting that GLP-1 may be able to

moderate diastolic dysfunction. (193) Ghrelin is involved in the modulation of the onset of myocardial relaxation and is thought to cause negative lusitropism; decreased levels of ghrelin after bariatric surgery are likely to contribute to an improved E/A ratio. (194, 195)

Speckle tracking analyses the degree of myocardial deformation throughout the cardiac cycle, known as strain. Specific ventricular segments are assessed, and speckles created by ultrasound are tracked throughout the cycle. Strain is calculated by measuring the differences in distance and velocity of the speckle during the cardiac cycle. (196) Strain is advantageous over EF as it allows for detection of myocardial dysfunction in the subclinical stage whereas changes in EF are a relatively late stage in the development of myocardial dysfunction. (196-198) In addition, systolic function measured by EF assesses radial fibres, however, longitudinal fibres are more sensitive than radial ones to ischaemic and hypertensive diseases. Speckle tracking avoids the angle dependent limitation of TDI and doesn't include geometric assumptions and volume dependence of EF. (33, 196, 198, 199) We found no significant difference in GLS or GCS between trimesters in either group. Longitudinal studies of deformation imaging in pregnancy are limited however, most show that in late pregnancy there is a significant decrease in global strain and one study showed no difference. (43, 52, 169, 200) When comparing the groups, we found that the GLS and GCS were significantly lower in the post-bariatric surgery group compared to the no-surgery group indicating better systolic performance in the former group. Studies of cardiovascular function after bariatric surgery, outside pregnancy, also show an improvement in GLS post-surgery where there is often no change in EF. (108-110, 201, 202) Interestingly, improvement in GLS has been found in individuals just one-month post-sleeve gastrectomy, although this was related to weight loss, this early difference in GLS suggests that there could be some metabolic influence via the entero-cardiac axis. (92, 93, 203) Secretin, glucagon and vasoactive intestinal peptide are gut hormones that act as inotropes via enzyme adenylate cyclase which is involved in cell communication. (91, 204) GLP-1 is known to improve insulin secretion post-bariatric surgery and is involved in cardiac modulation. (203) It has also been shown to improve LV systolic dysfunction after myocardial infarction and improve functional status in patients with chronic heart failure.(205, 206) Leptin levels correlate with LV mass and are reduced post-bariatric surgery which may also contribute to improved systolic performance. (188)

We found that the post-bariatric group had a significantly lower BW percentile than the no-surgery group. Pregnancy following bariatric surgery has been associated with an increased risk of delivering smaller babies and this is thought to be due to maternal malnourishment and micronutrient deficiencies. (111, 172) However, suppressed maternal CO has also been implicated as a potential mechanism in this pregnancy outcome. (58, 59) We found an overall positive correlation between maternal CO and BW percentile, but this was not the case when the groups were considered separately, perhaps due to the relatively small numbers in each group. More studies will be required to investigate further the role of maternal cardiovascular function in the development of PE and lower BW in pregnancies following bariatric surgery.

Conclusion

This study has found significant differences between the groups in haemodynamic function, diastolic indices and systolic function, despite our groups being closely matched for BMI. We found that bariatric surgery is associated with a more favourable maternal cardiovascular adaptation to pregnancy, which is likely to be independent of the weight loss alone. Cardiovascular changes in pregnant women after bariatric surgery, including better haemodynamic profile and diastolic/systolic indices, could render these women less susceptible to the development of hypertension and therefore, give some theory to the lower prevalence of hypertensive disorders seen in this population. Our study could also inform national guidance regarding beneficial effects of bariatric surgery in obese women of reproductive age contemplating pregnancy.

Chapter 5

Maternal cardiovascular adaptation in pregnancy in obese pregnant women compared to women with a normal body mass index

Abstract

Background: Normal pregnancy requires several cardiovascular adaptations to support the gravid uterus and maintain fetal growth. Maladaptation has been associated with the development of pre-eclampsia and studies have shown altered haemodynamic indices and cardiac function in the clinical and pre-clinical phase of the disease. Obesity is known to cause cardiovascular compromise outside of pregnancy and is major risk factor for the development of hypertensive disorders in pregnancy. Despite this there are limited studies investigating the effect of obesity on the maternal cardiovascular system.

Methods: This was a prospective, observational, longitudinal study. Women with BMI> 30 were compared to women with BMI 20-25 at their booking appointment. Participants were seen at three time points in pregnancy; 12-14, 20-24 and 30-32 weeks. Blood pressure (BP) was measured and maternal cardiac geometry and function were assessed using transthoracic echocardiography. Multilevel linear mixed-effects models were used for all the comparisons.

Results: 64 pregnant women with BMI>30 were compared to 14 pregnant women with BMI 20-25. The BP, heart rate and cardiac output were higher and total peripheral resistance was lower in the obese group ($p<0.01$ for all comparisons). The cardiac geometry differed with a higher left ventricle end diastolic diameter, intraventricular septal thickness, posterior wall diameter, left ventricular mass and left atrial diameter in the obese group ($p<0.001$ for all comparisons). Diastolic indices differed with a lower E/A ratio, tissue Doppler imaging E' lateral/medial and higher left atrial volume in the obese group ($p<0.01$ for all comparisons). There was a reduction in longitudinal function as assessed by mitral plane

annular systolic excursion between the second and third trimester in the obese group which was not the case in the normal BMI group.

Conclusions: Obesity is associated with a hyperdynamic circulation, altered cardiac geometry and reduced diastolic reserve; these factors may contribute to the increased risk of hypertensive disorders in obese pregnant women. Notably, both obesity and late pre-eclampsia share a hyperdynamic circulation with high cardiac output and low resistance in the pre-clinical phase.

Introduction

Obesity is a leading health concern and is associated with significant mortality and morbidity. (3) Obesity has several effects on the cardiovascular system with every 100g of fat deposited cardiac output (CO) is increased by 30–50 ml/min which is associated with an increase in stroke volume (SV) and heart rate (HR). High volume load leads to left ventricle (LV) dilation and then hypertrophy as the myocardium starts to dilate against increased pressure overload. This pressure is secondary to increased sympathetic activity due to the effects of hormones such as leptin, insulin and other inflammatory mediators. The HR and CO increase result in decreasing diastolic interval and therefore the time for myocardial perfusion. Impaired LV relaxation and compliance leads to diastolic dysfunction. The conduction and contractility can be further compromised when fat deposition occurs in the myocardial tissue. (93, 207) Although, diastolic function is impaired, systolic function commonly remains normal but in severe sustained obesity systolic dysfunction can also ensue. (6, 208)

Normal pregnancy is associated with significant maternal cardiovascular and haemodynamic changes that are needed to support fetal growth. Systemic vasodilation leads to a reduction in resistance and an increase in SV and CO. (28) In addition, there is a physiological eccentric remodelling with increased LV mass. Systolic function, measured by ejection fraction (EF), has been showed to be reduced compared to non-pregnant women however, it appears to remain unchanged during pregnancy. Diastolic reserve is reduced throughout gestation and there is evidence of dysfunction in around 25% of women at term. (37) In pregnancies complicated by pre-eclampsia (PE) or fetal growth restriction, cardiovascular changes have been reported in both the pre-clinical and clinical phase. (53, 55, 56)

Studies of the effect of obesity (BMI >30) on the maternal cardiovascular system are limited with varying results. Small cross-sectional studies in the third trimester (N=15 and N=8 obese subjects) have found an increase in LV mass, however, no change in CO or LV function. (70, 71) Another study of morbidly obese (BMI>40) pregnant women in the second or third trimester (N=23) found no difference in CO or SV, however when corrected for body surface area (BSA), both indices were lower in the morbidly obese group. Conversely, another study at term found higher CO and CI and lower resistance in the obese group (BMI>35, N=40), in addition, 40% of obese pregnant women had diastolic dysfunction together with a significant reduction in global longitudinal strain (GLS), a sensitive marker of systolic function, compared to pregnant women with a BMI<30. (72) A longitudinal study found that, compared to non-obese, obese pregnant women (N=232) demonstrate a high volume/low-resistance state in the first and second trimester, however, in the third trimester, the CO in the obese group decreased compared to the second trimester, and that a combination of volume changes due to pregnancy and pre-existing obesity lead to a high-volume state in mid gestation and subsequent volume overload in the third trimester. (74) These differences suggest a maladaptive cardiovascular response to pregnancy in obese women. To our knowledge this is the only longitudinal study of haemodynamic indices in obese pregnant women, however, they did not to investigate the maternal cardiovascular geometry and function, which can give more information and reflect the overall maternal cardiovascular adaptation to pregnancy. The few existing studies of geometry and function described above are cross-sectional rather than longitudinal and are mostly in the third trimester with varying results. The aim of the current study was to investigate longitudinally, the maternal haemodynamic indices, cardiac geometry and systolic and diastolic function in obese pregnant, compared to normal BMI, women.

Hypothesis

Pregnant obese women have an altered cardiovascular adaptation to pregnancy compared to women with normal BMI.

Aim

1. To compare, longitudinally, the maternal cardiovascular adaptation to pregnancy in women with BMI >30 with those of normal BMI. Maternal cardiovascular system

will be assessed using 2D echocardiography and will include cardiac geometry, haemodynamic variables, systolic, diastolic and longitudinal function.

2. To investigate the association of maternal haemodynamic function with BW.

Methods

This was a prospective, observational, longitudinal study. Pregnant women were recruited from April 2018 to June 2020 at Chelsea & Westminster Hospital, London, UK. Participants were identified through a booking-perinatal database (CIMIS). Following the 1st trimester scan, participants, with singleton pregnancies, were approached by members of the research team and recruited in the following groups:

- Group 1 – Pregnant women with early pregnancy BMI=20-25
- Group 2 – Pregnant women with early pregnancy BMI >30

Participants were seen at three time points during their pregnancy, 12-14, 20-24 and 30-32 weeks and women who attended at least two out of three research visits were included. Maternal characteristics, including age, parity, race, smoking status, method of conception and medication history were recorded in the research database. Maternal weight, height and manual blood pressure (BP) were measured and recorded. The maternal cardiovascular system was assessed using 2D echocardiography and haemodynamic variables, cardiac geometry, systolic, diastolic and longitudinal function, were evaluated, as previously described in Chapter 2. Pregnancy outcomes including development of diabetes or hypertensive disorders and delivery outcomes including gestation at delivery, mode of delivery and birthweight (BW) were obtained from the Hospital database. Birthweight percentiles, based on BW and gestation at delivery, were calculated.

Statistical analysis

The groups were compared at each time point and within each group the time points were compared using the unpaired Student t-test/Mann-Whitney or chi-square ($\chi 2$) for numerical and categorical data respectively. Differences were considered statistically significant at $p<0.05$.

Hierarchical modelling was used for further analysis of using multilevel linear mixed-effects models. The fixed effect component included time (the 3 visits), study group, age, race, diabetes status, smoking, gestation and first-order interaction between time and study group. The correlation of CO, total peripheral resistance (TPR) and mean arterial pressure (MAP) with birth weight (BW) were assessed by Pearson's correlation. All analyses were performed using IBM SPSS Statistics, version 26.0, 2019 (*IBM Corp., Armonk, New York, USA*).

Results

The study included 64 pregnant women with booking BMI >30 and 14 pregnant women with booking BMI 20-25. The maternal characteristics of the study population are given in Table 5.1.

Table 5.1. Maternal demographic characteristics and pregnancy outcomes of the study participants.

Variable	**BMI<25 N=14**	**BMI>30 N=64**	**P value**
Age (years)	34.2 (3.9)	33.0 (5)	0.32
Racial group			
White, n (%)	13 (93)	52 (82)	0.14
Other, n (%)	1 (7)	12 (18)	
Body mass index at booking (kg/m^2)	22.7 (2)	38.0 (6.1)	<0.001
Parity			
Nulliparous, n (%)	9 (64.3)	25 (39.1)	0.22
Parous, n (%)	5 (35.7)	39 (60.9)	
Conception			
Spontaneous, n (%)	13 (92.9)	56 (90.6)	0.57
Assisted reproductive technology, n (%)	1 (7.1)	8 (9.4)	
Smoking			

No, n (%)	14 (100)	61 (95.3)	0.41
Yes, n (%)	0 (0)	3 (4.7)	
Hypertensive disorders of pregnancy			
No, n (%)	14 (100)	59 (92.2)	0.28
Yes, n (%)	0 (0)	5 (7.8)	
Gestational diabetes mellitus			
No, n (%)	14 (100)	53 (82.8)	0.16
Yes, n (%)	0 (0)	11 (17.2)	
Mode of delivery			
Spontaneous vaginal delivery, n (%)	7 (50)	29 (45.3)	0.59
Operative vaginal delivery, n (%)	1 (7.1)	5 (7.8)	0.62
Caesarean section, n (%)	6 (42.9)	30 (46.9)	0.46
Gestational age at delivery (weeks)	39.9 (0.9)	38.8 (1.7)	0.02
Birth weight (grams)	3446 (325)	3501 (553)	0.87
Birthweight percentiles (%)	51 (25.1)	67 (28.6)	0.08

Data are expressed as mean (standard deviation), median (interquartile range) or n (%).

Hemodynamic variables

The median raw values of the haemodynamic variables in the three trimesters of pregnancy and comparisons between the groups are given in Table 5.2. Within each group the trimesters were compared and for significant differences, the mean difference and p values for trimester 1 vs 2, trimester 1 vs 3 and trimester 2 vs 3 are given in Table 5.3.

Table 5.2. Haemodynamic variables, median (interquartile range) for each trimester and group with p values of group comparison.

	1st Trimester 11-14 weeks			**2nd Trimester 20-24 weeks**			**3rd Trimester 30-32 weeks**		
	BMI 20-25 N=14	**BMI>30 N=64**	**P**	**BMI 20-25 N=14**	**BMI>30 N=64**	**P**	**BMI 20-25 N=14**	**BMI>30 N=64**	**P**
SBP (mmHg)	101.3 (100-105)	109 (101-119)	0.01	102 (91.8-106.5)	111 (99-116.8)	0.01	103 (97-103.3)	116.5 (101-117.6)	<0.01
DBP (mmHg)	60.5 (57.8-65.1)	64.5 (60-71)	0.01	59.5 (55.5-61.3)	62.5 (59-70)	<0.01	62 (58.5-64)	67 (60-69.3)	0.01
MAP (mmHg)	74.2 (72-77.8)	78.3 (73.8-86.3)	0.02	75.9 (68.1-76.8)	79.3 (73.3-85.1)	<0.01	77.7 (71.7-76.7)	83.3 (73.7-84.3)	0.01
HR (bpm)	72 (67-78.5)	82 (75-88)	<0.01	75.5 (66.5-80.5)	84 (75.3-91)	0.01	78 (68.5-89)	90 (82.8-98)	<0.01
SV (ml)	73.4 (66.9-79.6)	80.2 (71.3-93.1)	0.03	74.4 (69-82.9)	84.7 (75.2-102.8)	0.03	80.3 (71-84.8)	83.5 (76.7-97.5)	0.11
CO (L/min)	5.3 (4.5-6.1)	6.8 (5.7-7.5)	<0.001	6.0 (4.7-6.5)	7.0 (6.2-8.0)	<0.001	6.3 (5.1-6.9)	7.2 (6.2-9.0)	<0.01
TPR (dynes per s/cm)	1142.9 (959.8-1334.4)	977.4 (841.8-1159.7)	0.02	942.7 (881.7-1227.6)	889.5 (759-995.8)	0.06	1023 (794.2-1163.1)	925.5 (705.1-988.8)	0.03
SI (ml/BSA)	44.4 (39.9-48.4)	39.3 (36.1-42.9)	0.01	43.8 (39.8-51.5)	40.7 (37.2-46.8)	0.08	47.3 (43.3-50.6)	40.0 (35.5-46.3)	0.01
CI (l/BSA)	3.2 (2.6-3.9)	3.2 (2.8-3.6)	0.40	3.7 (2.7-3.9)	3.4 (3.1-3.7)	0.07	3.8 (3.1-4.4)	3.5 (3.1-4.4)	0.06

BSA, body surface area*; CO*, cardiac output; *CI* cardiac index; *DBP*, diastolic blood pressure; *HR*, heart rate; *MAP*, mean arterial pressure; *SV*, stroke volume; *SVI*, stroke volume index; *SBP*, systolic blood pressure; *TPR*, total peripheral resistance

Table 5.3. Mean difference of haemodynamic variables between trimesters in the two groups of women (actual values given in Table 5.2). All comparisons have been adjusted by the Bonferroni correction for multiple tests. (T1: 11-14 weeks, T2: 20-24 weeks, T3: 30-32 weeks)

BMI 20-25						
	T 1 vs 2		T 1 vs 3		T 2 vs 3	
	Mean difference	P	Mean difference	P	Mean difference	P
HR (bpm)	2.5 (7.7)	0.8	7 (10.3)	**<0.01**	4.5 (8.3)	0.33
CO (L/min)	0.4 (0.9)	0.25	0.9 (1.2)	**<0.01**	0.5 (1.3)	0.52
TPR (dynes per s/cm)	-114 (173.3)	0.08	-159.4 (203.2)	**<0.05**	-41.2 (263.3)	0.62
CI (ml/BSA)	0.3 (0.5)	0.54	0.2 (0.9)	**0.02**	0 (1.3)	0.4
BMI>30						
	T 1 vs 2		T 1 vs 3		T 2 vs 3	
	Mean difference	P	Mean difference	P	Mean difference	P
HR (bpm)	2.3 (11.1)	0.31	7.5 (9.6)	**<0.01**	5.9 (10.7)	<0.01
CO (L/min)	0.5 (1.1)	0.06	1 (1.6)	**<0.01**	0.5 (1.6)	0.22
TPR (dynes per s/cm)	-75.3 (201.3)	**0.02**	-134.8 (237.8)	**<0.01**	-56.3 (227.9)	0.17
CI (ml/BSA)	0.2 (0.5)	0.05	0.5 (0.8)	**<0.01**	0.2 (0.8)	0.19

BSA, body surface area*; CO*, cardiac output; *CI* cardiac index; *HR*, heart rate; *TPR*, total peripheral resistance

Mixed model analysis was used to compare the haemodynamic variables between groups at each trimester and overall, after adjustment for age, race, gestational age, diabetes status and smoking. The overall group comparison across all trimesters is given in Table 5.4 and the estimated marginal means at each trimester for each group is given in Table 5.5.

Table 5.4 Multilevel linear mixed-effects models for Log10 haemodynamic variables, overall group comparison across all trimesters

Overall group comparisons (All trimesters)		
	Mean Difference BMI>30 – BMI 20-25 (95% Confidence Interval for Difference)	**P**
SBP (mmHg)	0.04 (0.02-0.04)	**<0.001**
DBP (mmHg)	0.06 (0.01-0.05)	**<0.01**
MAP (mmHg)	0.04 (0.01-0.04)	**<0.001**
HR (bpm)	0.04 (0.02-0.06)	**<0.001**
SV (ml)	0.04 (0.01-0.07)	**0.01**
CO (L/min)	0.08 (0.05-0.12)	**<0.001**
TPR (dynes per s/cm)	-0.05 (-0.09-(-0.02))	**<0.01**
SI (ml/BSA)	-0.05 (-0.08-(-0.03))	**<0.01**
CI (ml/BSA)	-0.02 (-0.05-0.02)	0.31

BSA, body surface area*; CO*, cardiac output; *CI* cardiac index; *DBP*, diastolic blood pressure; *HR*, heart rate; *MAP*, mean arterial pressure; *SV*, stroke volume; *SVI*, stroke volume index; *SBP*, systolic blood pressure; *TPR*, total peripheral resistance

Table 5.5. Multilevel linear mixed-effects models for Log10 hemodynamic variables. Estimated marginal means (95% CI) for each trimester and group are given.

	1st Trimester 11-14 weeks			2nd Trimester 20-24 weeks			3rd Trimester 30-32 weeks		
	BMI 20-25 N=14	**BMI>30 N=64**	**P**	**BMI 20-25 N=14**	**BMI>30 N=64**	**P**	**BMI 20-25 N=14**	**BMI>30 N=64**	**P**
Log_{10} SBP (mmHg)	2.03 (2.01-2.06)	2.06 (2.05-2.08)	**0.01**	2.05 (2-2.05)	2.08 (2.04-2.07)	**0.01**	2.07 (2.01-2.06)	2.11 (2.04-2.07)	**<0.01**
Log_{10} DBP (mmHg)	1.8 (1.77-1.84)	1.83 (1.8-1.84)	**0.01**	1.78 (1.75-1.81)	1.82 (1.8-1.84)	**0.01**	1.8 (1.77-1.83)	1.85 (1.8-1.84)	**<0.01**
Log_{10} MAP	1.89 (1.87-1.92)	1.92 (1.9-1.94)	**0.02**	1.88 (1.85-1.9)	1.91 (1.9-1.93)	**0.01**	1.89 (1.87-1.92)	1.95 (1.9-1.93)	**0.01**
Log_{10}HR (bpm)	1.9 (1.87-1.94)	1.94 (1.92-1.96)	**0.02**	1.92 (1.88-1.95)	1.95 (1.93-1.97)	**0.02**	1.94 (1.9-1.97)	1.99 (1.96-2)	**<0.01**
Log_{10} SV (ml)	1.86 (1.81-1.92)	1.91 (1.87-1.94)	**0.01**	1.88 (1.82-1.94)	1.93 (1.89-1.96)	**0.01**	1.89 (1.83-1.94)	1.92 (1.89-1.96)	0.06
Log_{10} CO (l/min)	3.76 (3.7-3.82)	3.84 (3.81-3.88)	**<0.01**	3.79 (3.73-3.85)	3.87 (3.84-3.91)	**0.01**	3.83 (3.76-3.89)	3.89 (3.86-3.94)	**0.02**
Log_{10} TPR (dynes per s/cm)	3.04 (2.98-3.09)	2.98 (2.95-3.01)	**0.03**	2.99 (2.93-3.05)	2.94 (2.91-2.98)	**0.02**	2.97 (2.91-3.03)	2.91 (2.88-2.95)	**0.03**
Log_{10} SVI (ml/BSA)	1.63 (1.58-1.68)	1.58 (1.55-1.61)	0.05	1.65 (1.59-1.7)	1.60 (1.57-1.63)	0.08	1.66 (1.61-1.7)	1.60 (1.57-1.63)	**0.02**
Log_{10} CI (ml/BSA)	3.53 (3.48-3.58)	3.52 (3.49-3.55)	0.71	3.56 (3.51-3.62)	3.55 (3.51-3.58)	0.78	3.59 (3.53-3.65)	3.56 (3.54-3.61)	0.07

BSA, body surface area*; CO*, cardiac output; *CI* cardiac index; *DBP*, diastolic blood pressure; *HR*, heart rate; *MAP*, mean arterial pressure; *SV*, stroke volume; *SVI*, stroke volume index; *SBP*, systolic blood pressure; *TPR*, total peripheral resistance

In summary, within each group there was an upward trend in systolic blood pressure (SBP) across trimesters. Diastolic blood pressure (DBP) and mean arterial pressure (MAP) trended down in the second trimester and then increased in the third trimester, however there were no significant differences between trimesters in either group. Between groups, the obese group had a higher SBP, DBP and MAP in all trimesters and overall, compared to the normal BMI group. (Tables 5.4, 5.5 and Figure 5.1).

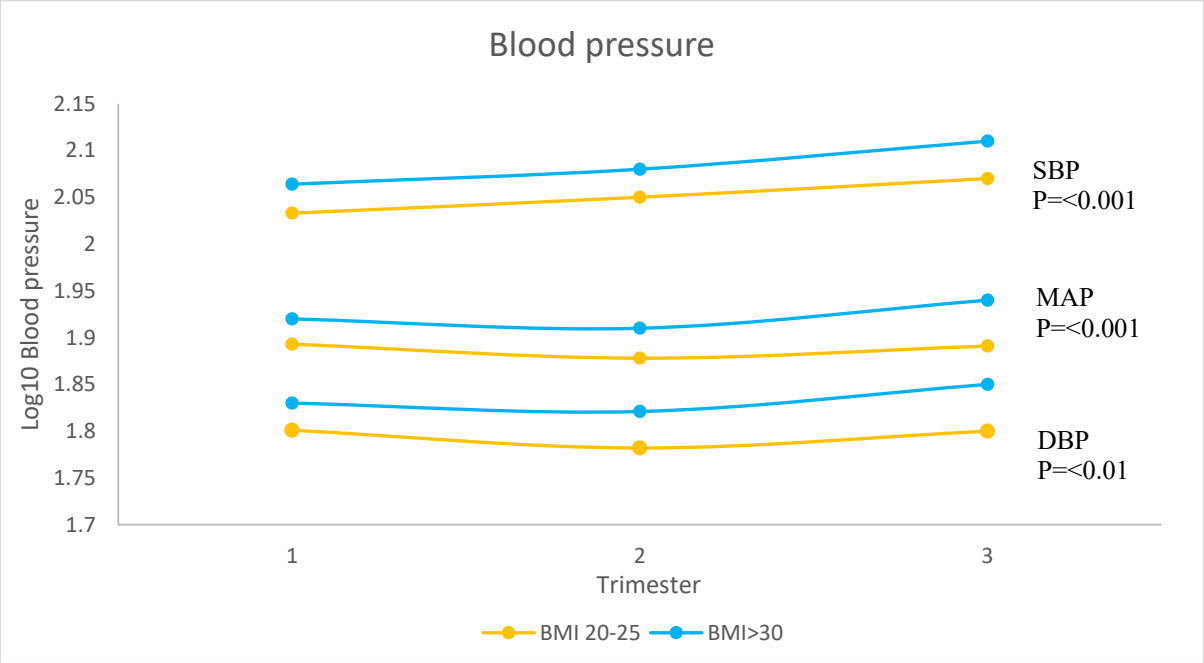


Figure 5.1. Mixed model analysis systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP) across trimesters in both groups.

Maternal HR was higher in the third compared to first trimester in both groups and higher, in all trimesters, in the obese compared to the normal BMI group (Tables 5.4, 5.5 and Figure 5.2).

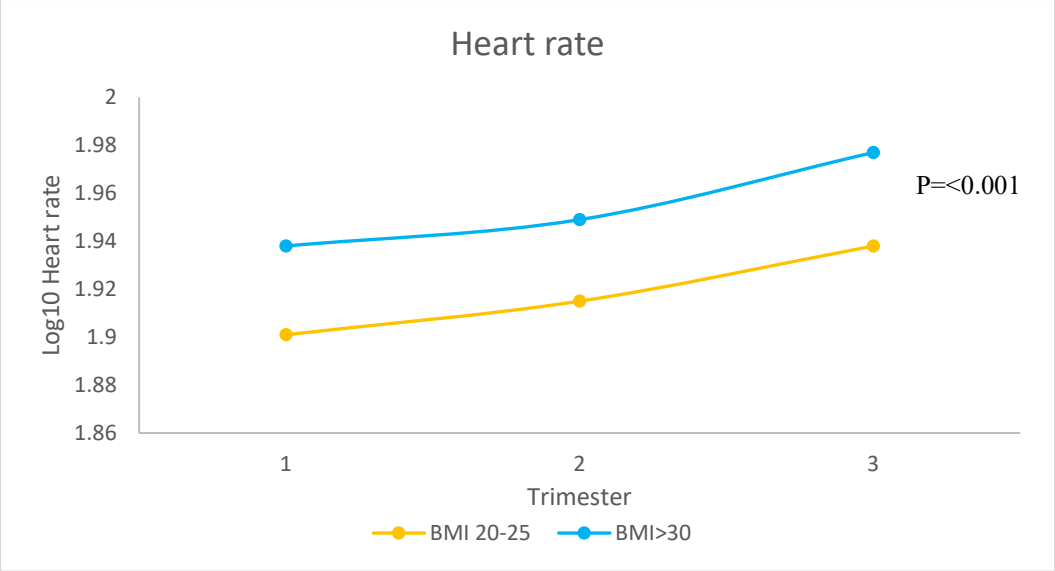


Figure 5.2. Mixed model analysis for heart rate across trimesters in both groups

The SV and CO trended up in both groups with a significant increase in CO in the third compared to the first trimester. Between the second and third trimester there was a non-significant increase in SV in the normal BMI group however a plateau in the obese group. When comparing the groups, overall, the CO and SV were significantly higher in the obese compared to the normal BMI group (Table 5.4, Figure 5.3). Conversely, when corrected for BSA, the SVI was significantly lower and CI non-significantly lower in the obese, compared to the normal BMI, group but only in the third trimester (Table 5.5, Figure 5.4).

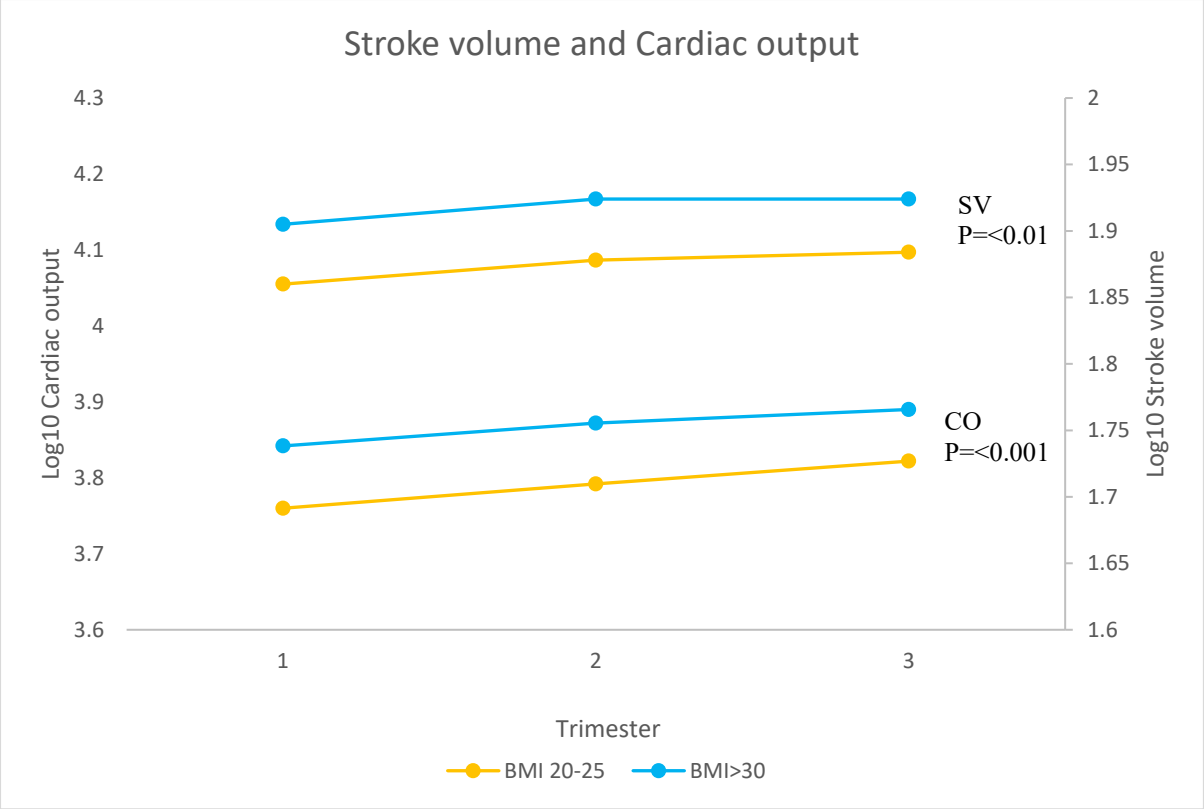


Figure 5.3. Mixed model analysis for stroke volume (SV) and cardiac output (CO) across trimesters in both groups

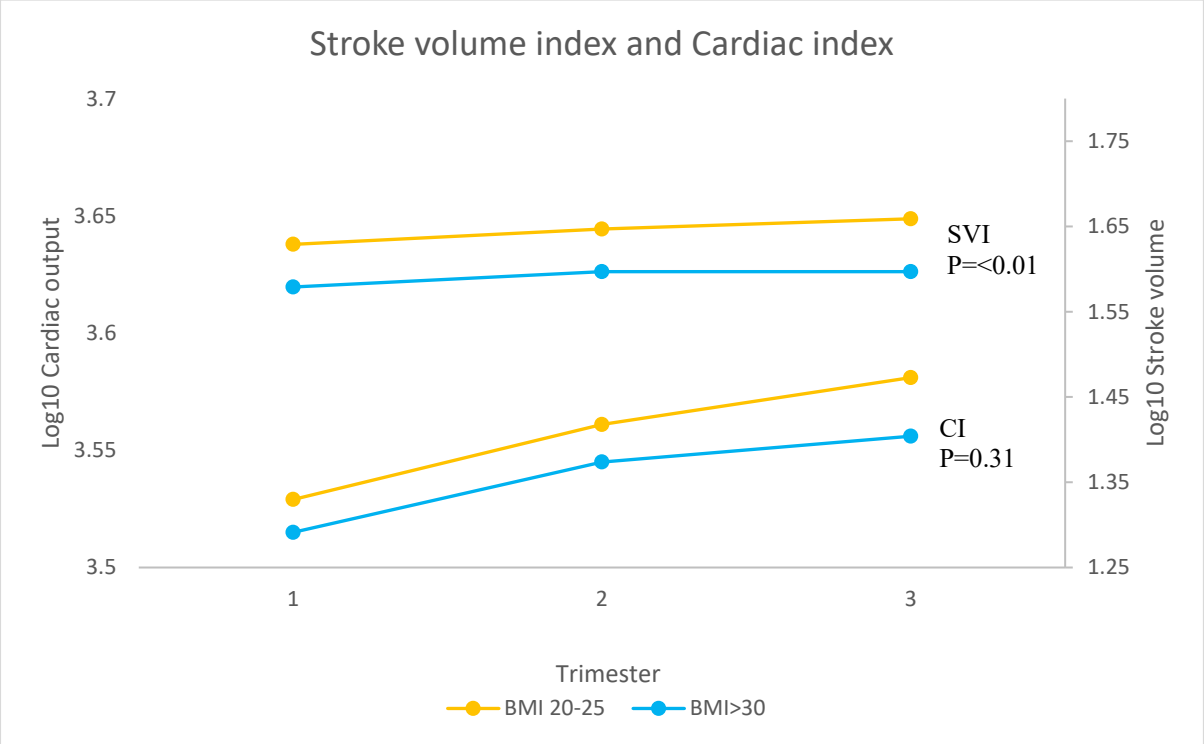


Figure 5.4. Mixed model analysis for stroke volume index (SV) and cardiac index (CI) across trimesters in both groups

The total peripheral resistance (TPR) trended down across trimesters in both groups and was significantly lower in the third compared to first trimester. When comparing the groups, the TPR was lower in the obese compared to the normal BMI group (Table 5.4, Figure 5.5).

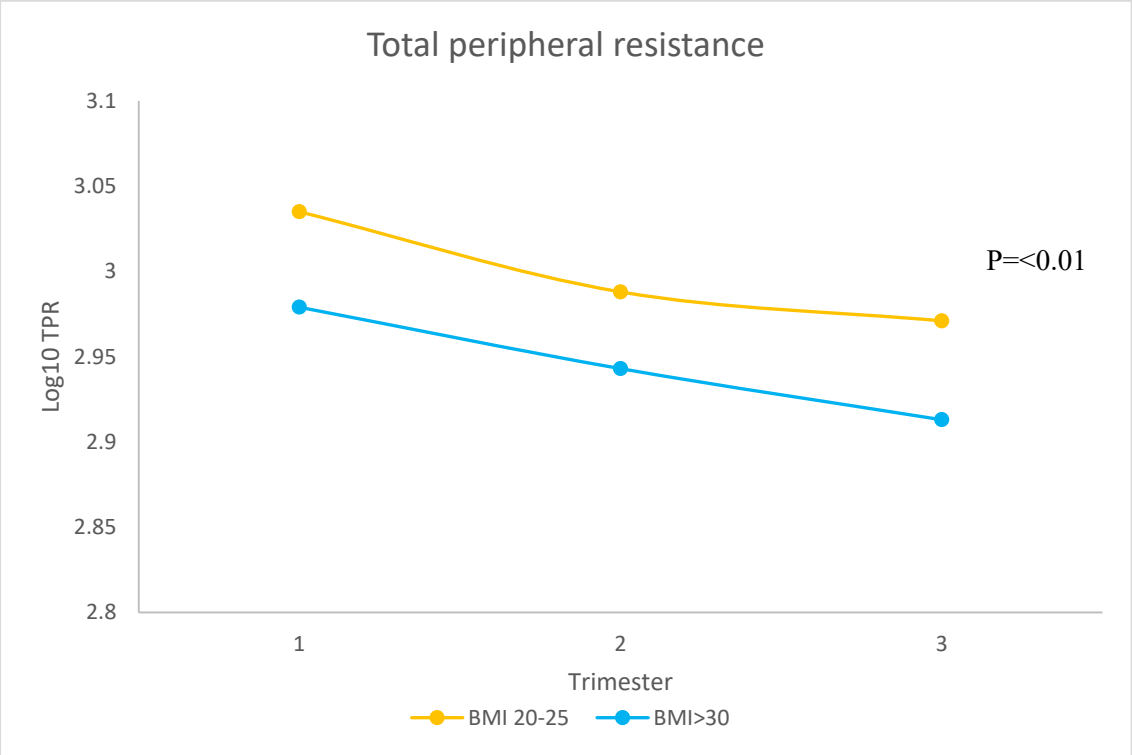


Figure 5.5. Mixed model analysis for total peripheral resistance (TPR) across trimesters in both groups

Cardiac geometry

The mean raw values of the cardiac geometry in the three trimesters of pregnancy and comparisons between the groups are given in Table 5.6. Within each group the trimesters were compared and for significant differences, the mean difference and p values for trimester 1 vs 2, trimester 1 vs 3 and trimester 2 vs 3 are given in Table 5.7.

Table 5.6. Cardiac geometry, mean (standard deviation) for each trimester and group with p values of group comparison

	1st Trimester 11-14 weeks			**2nd Trimester 20-24 weeks**			**3rd Trimester 30-32 weeks**		
	BMI 20-25 N=14	**BMI>30 N=64**	**P**	**BMI 2-0-25 N=14**	**BMI>30 N=64**	**P**	**BMI 20-25 N=14**	**BMI>30 N=64**	**P**
LA (mm)	35.5 (3.4)	39.6 (4.7)	**<0.01**	36.6 (3.2)	40.3 (5.2)	**0.02**	37.6 (4.5)	40.1 (4.2)	**0.02**
LA index (mm/BSA)	21.3 (2.1)	18.9 (2.3)	**<0.01**	22.6 (2.2)	19.3 (2.5)	**<0.01**	22.1 (3)	19.2 (2.1)	**0.01**
Aorta (mm)	25.1 (2.5)	27.5 (2.8)	**<0.01**	24.4 (2.3)	27.5 (3)	**<0.01**	25.5 (1.8)	27.6 (3.4)	**<0.01**
Ascending aorta (mm)	25.9 (2.5)	27.9 (3.4)	**0.02**	25.1 (2.5)	28 (2.7)	**<0.01**	26.2 (2)	28.1 (2.8)	**0.01**
LVOT (mm)	19.2 (0.9)	20.6 (1.6)	**<0.001**	19.7 (1.2)	20.9 (1.8)	**<0.01**	19.9 (1)	21.2 (1.7)	**<0.01**
IVS (mm)	6.9 (1.2)	8.5 (1.5)	**<0.001**	6.9 (1.4)	8.8 (1.4)	**<0.01**	7.7 (0.8)	9.1 (1.3)	**<0.01**
LVEDD (mm)	45.8 (2.5)	48.7 (5.4)	**<0.01**	46.8 (3.2)	50.3 (4.9)	**<0.01**	46 (3.9)	50.4 (5.3)	**<0.01**
LVEDD index (mm/BSA)	27.5 (2.3)	23.4 (2.7)	**<0.001**	28.1 (3)	24.1 (2.6)	**<0.01**	27.7 (2.8)	24.3 (2.7)	**<0.01**
PW (mm)	7.1 (1.2)	9.1 (1.5)	**<0.001**	7.6 (1.6)	9.2 (1.4)	**<0.01**	8.2 (0.8)	10 (1.5)	**<0.01**
RWT	0.31 (0.06)	0.38 (0.08)	**<0.01**	0.33 (0.08)	0.37 (0.07)	**0.04**	0.36 (0.04)	0.4 (0.07)	**0.01**
LVM (g)	101.8 (21.2)	152.7 (35.8)	**<0.001**	110.2 (27.1)	165.5 (35.8)	**<0.01**	120.9 (20.4)	179.5 (41.6)	**<0.01**
LVM index (g/BSA)	61.3 (13.9)	72.7 (14.3)	**0.01**	66.1 (16.4)	78.5 (14.2)	**0.02**	72.9 (12.8)	85.7 (18.2)	**0.01**

BSA, body surface area*; IVS*, interventricular septum; *LA*, left atrium diameter; *LVEDD*, left ventricle end-diastolic diameter; *LVM*, left ventricular mass; *LVOT*, left ventricle outflow tract; *PW*, posterior wall thickness; *RWT*, relative wall thickness; *BSA*, body surface area

Table 5.7. Mean difference in cardiac geometry between trimesters in the two groups of women (actual values given in Table 5.6). All comparisons have been adjusted by the Bonferroni correction for multiple tests. (T1: 11-14 weeks, T2: 20-24 weeks, T3: 30-32 weeks)

BMI 25-30						
	T 1 vs 2		T 1 vs 3		T 2 vs 3	
	Mean difference	P	Mean difference	P	Mean difference	P
IVS (mm)	0 (1.8)	0.98	0.8 (1.4)	0.06	0.8 (1.7)	0.12
PW (mm)	0.5 (1.1)	0.48	1.2 (1.3)	**0.01**	0.6 (1.6)	0.11
RWT	0.02 (0.05)	0.73	0.05 (0.06)	**0.03**	0.02 (0.08)	0.16
LVM (g)	8.9 (20.9)	0.4	18 (20.3)	**0.03**	9.1 (22)	0.16
LVM index (g/BSA)	5 (12)	0.7	10.7 (11.5)	**0.03**	5.7 (13.4)	0.09
BMI>30						
	T 1 vs 2		T 1 vs 3		T 2 vs 3	
	Mean difference	P	Mean difference	P	Mean difference	P
IVS (mm)	0.3 (1.6)	0.18	0.6 (2.3)	**<0.01**	0.2 (1.7)	0.08
PW (mm)	0.2 (1.8)	0.75	1.1 (2)	**<0.001**	0.8 (1.5)	**0.01**
RWT	0.01 (0.07)	0.66	0.02 (0.08)	0.09	0.03 (0.07)	**0.03**
LVM (g)	9.9 (23.1)	0.05	25.9 (33.2)	**<0.001**	16 (30)	0.05
LVM index (g/BSA)	4.9 (10.8)	0.05	12.6 (16.1)	**<0.001**	7.8 (14.4)	**0.03**

BSA, body surface area*; IVS*, interventricular septum; *LVM*, left ventricular mass; *PW*, posterior wall thickness; *RWT*, relative wall thickness

Mixed model analysis was used to compare the cardiac geometry between groups at each trimester and overall, after adjustment for age, race, gestational age, diabetes status and smoking. The overall group comparison across all trimesters is given in Table 5.8 and the estimated marginal means at each trimester for each group is given in Table 5.9.

Table 5.8. Multilevel linear mixed-effects models for cardiac geometry, overall group comparison across all trimesters

Overall group comparisons (All trimesters)		
	Mean Difference, BMI>30 – BMI 20-25 (95% Confidence Interval for Difference)	**P**
LA (mm)	3.3 (1.7-4.8)	**<0.001**
LA index (mm)	-2.8 (-3.6-(-2))	**<0.001**
IVS (mm)	1.4 (0.9-1.8)	**<0.001**
LVEDD (mm)	3.7 (2-5.5)	**<0.001**
LVEDD index (mm/BSA)	-3.7 (-4.6-(-2.7))	**<0.001**
PW (mm)	1.8 (1.3-2.3)	**<0.001**
RWT	0.05 (0.03-0.08)	**<0.001**
LVM (g)	51.9 (39.4-64.5)	**<0.001**
LVM index (g/BSA)	11.6 (6.1-17)	**<0.001**

BSA, body surface area*; IVS*, interventricular septum; *LA*, left atrium diameter; *LVEDD*, left ventricle end-diastolic diameter; *LVM*, left ventricular mass; *PW*, posterior wall thickness; *RWT*, relative wall thickness; *BSA*, body surface area

Table 5.9. Multilevel linear mixed-effects models for cardiac geometry, estimated marginal means (95% CI) for each trimester and group are given.

	1st Trimester 11-14 weeks			**2nd Trimester 20-24 weeks**			**3rd Trimester 30-32 weeks**		
	BMI <25 N=14	**BMI>30 N=64**	**P**	**BMI <25 N=14**	**BMI>30 N=64**	**P**	**BMI <25 N=14**	**BMI>30 N=64**	**P**
LA (mm)	35.6 (33.9-39.3)	39.1 (38.9-41.9)	**0.01**	36.8 (36-41.6)	40.1 (39.5-42.6)	**0.03**	37.8 (35.1-40.4)	41 (39.5-42.5)	**0.02**
LA index (mm)	21.3 (19.9-22.8)	19 (18.2-19.8)	**<0.01**	22.7 (21.2-24.1)	19.3 (18.5-20.1)	**<0.001**	22.1 (20.7-23.5)	19.2 (18.5-20)	**<0.001**
IVS (mm)	7.7 (6.9-8.6)	9.1 (8.6-9.6)	**<0.01**	7.7 (6.9-8.5)	9.4 (8.9-9.8)	**<0.001**	8.6 (7.8-9.3)	9.7 (9.3-10.2)	**<0.01**
LVEDD (mm)	45.1 (42-48.1)	48.2 (46.5-49.9)	**<0.05**	46.1 (43.1-49)	49.8 (48.1-51.4)	**0.03**	46.4 (42.1-48.6)	49.9 (48-51.5)	**0.01**
LVEDD index (mm/BSA)	26.6 (25-28.2)	22.7 (21.8-23.6)	**<0.001**	27.2 (25.5-28.9)	23.4 (22.4-24.3)	**<0.001**	27.8 (25-28.6)	23.6 (22.6-24.6)	**<0.01**
PW (mm)	7.2 (6.3-8.1)	9.2 (8.8-9.7)	**<0.001**	7.7 (6.8-8.6)	9.4 (8.9-9.9)	**<0.001**	8.3 (7.5-9.2)	10.1 (9.7-10.6)	**<0.001**
RWT	0.32 (0.27-0.36)	0.38 (0.36-0.41)	**0.01**	0.33 (0.29-0.38)	0.39 (0.35-0.40)	**0.04**	0.37 (0.32-0.41)	0.41 (0.38-0.43)	**0.03**
LVM (g)	110.6 (89.3-132)	158.7 (146.7-170.7)	**<0.001**	119.1 (98.2-140)	171.8 (160-183.6)	**<0.001**	125.1 (106.2-154.1)	180 (172.9-199)	**<0.001**
LVM index (g/BSA)	63 (53.8-72.3)	73.7 (68.6-78.9)	**0.03**	67.8 (58.9-76.8)	79.7 (74.7-84.8)	**0.01**	71.6 (64-85.2)	87 (81.3-92.7)	**0.01**

BSA, body surface area*; IVS*, interventricular septum; *LA*, left atrium diameter; *LVEDD*, left ventricle end-diastolic diameter; *LVM*, left ventricular mass; *PW*, posterior wall thickness; *RWT*, relative wall thickness; *BSA*, body surface area

Table 5.10. Percentage of participants with left ventricle hypertrophy in each trimester and group

	1st Trimester 11-14 weeks		P	**2nd Trimester 20-24 weeks**		P	**3rd Trimester 30-32 weeks**		P
	BMI 20-25	BMI >30		BMI 20-25	BMI >30		BMI 20-25	BMI >30	
Hypertrophy (RWT>0.42 and LVM index>95g/m^2)	0% (0)	9% (6)	<0.01	7% (1)	22% (14)	<0.01	7% (1)	19% (12)	<0.01

LVM index, left ventricular mass/body surface area; *RWT*, relative wall thickness

In summary, there was a significant increase with gestation in posterior wall thickness (PWT), relative wall thickness (RWT), LV mass and LV mass index in both groups (Table 5.7). The left atrial (LA) diameter, LA diameter index, interventricular septum (IVS), left ventricle end-diastolic diameter (LVEDD), LVEDD index all trended upwards in both groups. When comparing the groups, the LA diameter, IVS, LVEDD, PWT, RWT, LV mass and LV mass index were all higher in the obese group (Tables 5.8, 5.9 and Figures 5.6 and 5.7). The prevalence of concentric LV hypertrophy (RWT>0.42 and LV mass index >95g/m^2) was higher in the obese group in all trimesters (Table 5.10).

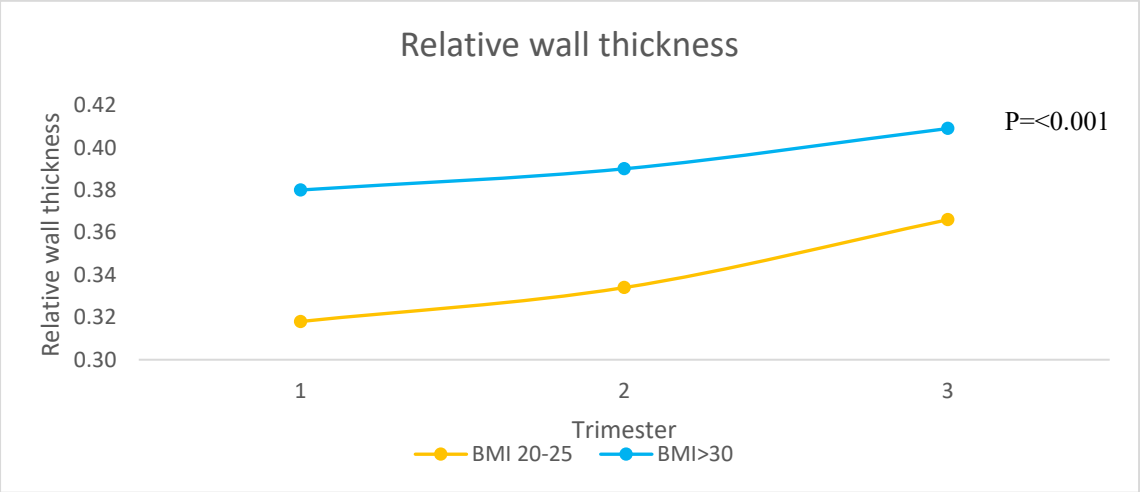


Figure 5.6. Mixed model analysis for relative wall thickness across trimesters in both groups

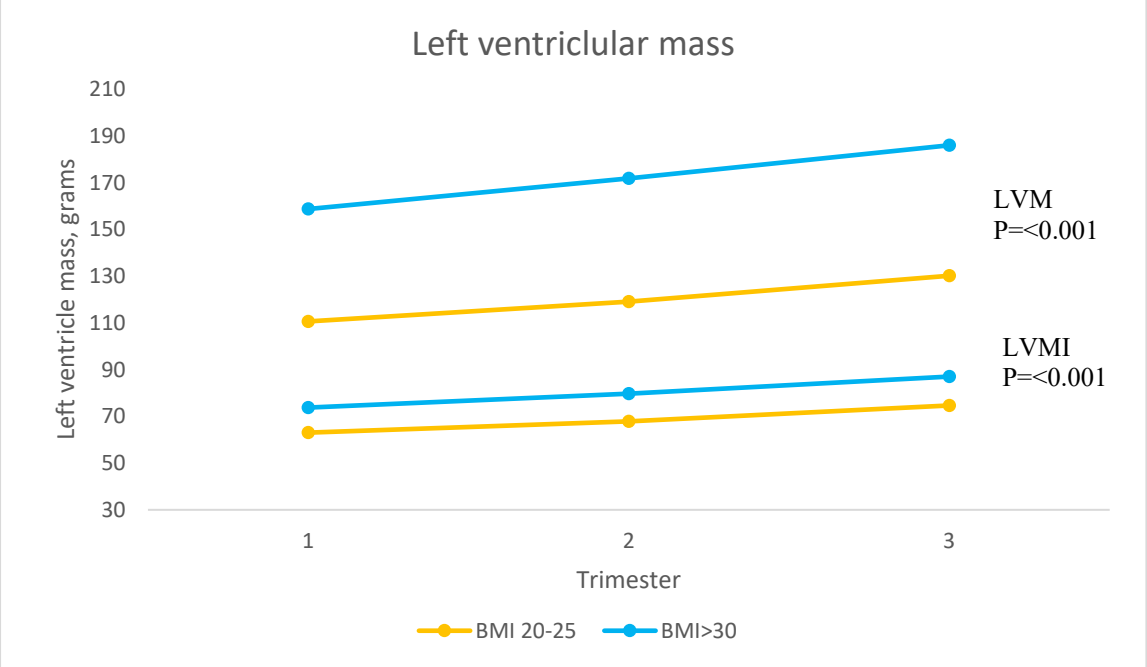


Figure 5.7. Mixed model analysis of left ventricular mass (LVM) and left ventricular mass index (LVMI) across trimesters in both groups

Systolic, diastolic and longitudinal function

The mean raw values of the systolic, diastolic and longitudinal function in each trimester and comparisons between the groups are given in Table 5.11. Within each group the trimesters were compared and for significant differences, the mean difference and p values for trimester 1 vs 2, trimester 1 vs 3 and trimester 2 vs 3 are given in Table 5.12.

Table 5.11. Systolic, diastolic and longitudinal function, mean (standard deviation) for each time point and group with p values.

	1st Trimester 11-14 weeks			**2nd Trimester 20-24 weeks**			**3rd Trimester 30-32 weeks**		
	BMI 20-25, N=14	**BMI>30, N=64**	**P**	**BMI 20-25, N=14**	**BMI>30, N=64**	**P**	**BMI 20-25, N=14**	**BMI>30, N=64**	**P**
Systolic function									
EDV (mm)	79.9 (17.7)	98.1 (19.6)	**<0.001**	81.5 (15.5)	99.1 (19)	**<0.01**	83.4 (12.2)	100.7 (21.8)	**<0.01**
EDV index (mm/BSA)	48 (10.7)	46.6 (7.6)	0.66	48.9 (9.5)	47.1 (7.3)	0.51	50.1 (6.4)	47.8 (8.2)	0.27
ESV (mm)	31 (9.3)	39.6 (9.7)	**0.01**	31.6 (10.2)	39.9 (10.5)	**0.01**	32.6 (8.1)	41.5 (10.9)	**<0.01**
ESV index (mm/BSA)	18.7 (5.8)	18.8 (3.8)	0.93	19 (6.4)	18.9 (4.3)	0.95	19.6 (4.6)	19.7 (4.4)	0.95
EF (%)	62.4 (5.9)	60.3 (4.6)	0.22	61.6 (6.6)	59.9 (5.3)	0.39	61.5 (5.3)	59.8 (4.4)	0.29
TDI s' (cm)	13.9 (1.8)	12.8 (2.3)	0.05	14.7 (2.2)	13.4 (2.5)	0.10	13.9 (2.1)	13.7 (3)	0.79
Diastolic function									
E/A ratio	1.80 (0.21)	1.41 (0.33)	**0.01**	1.71 (0.32)	1.35 (0.34)	**0.01**	1.63 (0.40)	1.22 (0.35)	**0.01**
E' lateral (m/s)	16.7 (4.3)	14.4 (3)	**0.01**	15.6 (3.6)	13.4 (3.1)	**0.03**	13.5 (2.7)	12.9 (2.9)	0.50
E' medial (m/s)	11.8 (1.7)	10 (2.2)	**<0.01**	10.8 (1.8)	10.1 (2.6)	0.25	10.2 (2.3)	9.2 (2.1)	0.17
E/ E' ratio	5.9 (1.4)	6.7 (1.6)	0.04	6.2 (1.5)	7.1 (1.5)	0.05	6.7 (1.6)	7.1 (2.2)	0.37
LAV (ml)	55.6 (12.2)	60.8 (13.5)	**0.01**	57 (8.5)	64.2 (12.4)	**<0.01**	57.8 (10.5)	64.5 (15.6)	**0.01**
LAV index (ml/BSA)	32.3 (8.5)	31.1 (5.6)	0.09	34.2 (9.4)	31.5 (5.5)	0.07	34.1 (7.1)	31.8 (6.7)	0.06
Longitudinal function									
TAPSE (mm)	25.3 (3.6)	22.5 (3.4)	**0.02**	26.3 (3.4)	23.5 (4.4)	**0.02**	25.4 (3.5)	22.1 (4.3)	**0.01**
MAPSE septal (mm)	14.6 (2.1)	15.3 (2.8)	0.28	14.2 (3.2)	14.1 (1.9)	0.89	14.1 (3.3)	13 (2.1)	0.29
MAPSE lateral (mm)	16.1 (2)	16.4 (3.1)	0.62	14.7 (2.1)	16.3 (3.3)	0.06	15.3 (2.1)	14.7 (3.1)	0.61

BSA, body surface area*; E/A ratio*, mitral inflow E-wave/A-wave filling; *E' lateral*, tissue Doppler imaging E prime measured at lateral mitral annulus; *E' medial*, tissue Doppler imaging E prime measured at medial mitral annulus; *E/E' ratio*, E-wave mitral inflow/ mean E' lateral and E' medial; *EF*, ejection fraction; *EDV*, end-diastolic volume; *LAV*, left atrial volume; *ESV*, end-systolic volume; *TDI s'*, tissue Doppler imaging s' at the lateral tricuspid annulus; *MAPSE*, mitral annular plane systolic excursion; *TAPSE*, tricuspid annular plane systolic excursion

Table 5.12. Mean difference in diastolic and longitudinal function between trimesters in the two groups of women (actual values given in Table 5.11). All comparisons have been adjusted by the Bonferroni correction for multiple tests. (T1: 11-14 weeks, T2: 20-24 weeks, T3: 30-32 weeks)

BMI 20-25						
	T 1 vs 2		T 1 vs 3		T 2 vs 3	
	Mean difference	P	Mean difference	P	Mean difference	P
Diastolic function						
E/A ratio	-0.1(0.4)	0.35	-0.2 (0.5)	**0.04**	-0.1 (0.4)	0.79
E' lateral (m/s)	-1.1(3.9)	0.48	-0.3(5.2)	**0.03**	-1.5(3.0)	0.17
Longitudinal function						
MAPSE septal (mm)	-0.1(2.1)	0.91	-0.4 (2.2)	0.46	-0.1(1.5**)**	0.72
MAPSE lateral (mm)	-0.2(2.1)	0.11	-0.5 (2.7)	0.07	0.1(1.5**)**	0.65
BMI>30						
	T 1 vs 2		T 1 vs 3		T 2 vs 3	
	Mean difference	P	Mean difference	P	Mean difference	P
Diastolic function						
E/A ratio	-0.1(0.3)	0.21	-0.3(0.6)	**<0.01**	-0.1(0.3)	**0.03**
E' lateral (m/s)	-0.6(3.6)	0.05	-1.2(3.8)	**0.01**	-0.7(3.4)	0.46
Longitudinal function						
MAPSE septal (mm)	-0.4(2.1)	0.06	-0.7 (2.7)	**<0.01**	-1.4(1.5**)**	**<0.01**
MAPSE lateral (mm)	-0.1 (2.0)	0.73	-(0.9) 2.4	**<0.01**	-0.7 (2.3)	**0.01**

E/A ratio, mitral inflow E-wave/A-wave filling; *E' lateral*, tissue Doppler imaging E prime measured at lateral mitral annulus; *MAPSE*, mitral annular plane systolic excursion

Mixed model analysis was used to compare the systolic and diastolic function between groups at each trimester and overall, after adjustment for age, race, gestational age, diabetes status and smoking. The overall group comparison across all trimesters is given in Table 5.13 and the estimated marginal means at each trimester for each group are given in Table 5.14.

Table 5.13. Multilevel linear mixed-effects models for systolic, diastolic and longitudinal, function, overall group comparison across all trimesters.

Overall group comparisons (All trimesters)		
	Mean Difference BMI>30 – BMI 20-25 (95% Confidence Interval for Difference)	**P**
Systolic function		
EDV (mm)	15.71 (8.7-22.71)	**<0.001**
EDV index (mm/BSA)	-2.43 (-5.3-0.45)	0.10
ESV (mm)	7.52 (3.87-11.16)	**<0.001**
ESV index (mm/BSA)	-0.31 (-1.9-1.28)	0.70
EF (%)	-1.47 (-3.24-0.31)	0.10
TDI s' (cm)	-1.02 (-1.94-(-0.1))	**0.03**
Diastolic function		
E/A ratio	-0.28 (-0.38-(-0.17))	**<0.001**
E' lateral (m/s)	-1.97 (-3.06-(-0.88))	**<0.001**
E' medial (m/s)	-1.36 (-2.13-(-0.58))	**<0.001**
E/ E' ratio	0.68 (0.08-1.29)	**0.03**
LAV (ml)	12.14 (7.37-16.92)	**<0.01**
LAV index (ml/BSA)	-1.43 (-3.77-0.92)	0.23
Longitudinal function		
TAPSE (mm)	-2.79 (-4.21-(-1.37))	**<0.001**
MAPSE septal (mm)	-0.13 (-0.74-1)	0.77
MAPSE lateral (mm)	-0.72 (-0.36-1.8)	0.19

BSA, body surface area*; E/A ratio*, mitral inflow E-wave/A-wave filling; *E' lateral*, tissue Doppler imaging E prime measured at lateral mitral annulus; *E' medial*, tissue Doppler imaging E prime measured at medial mitral annulus; *E/E' ratio*, E-wave mitral inflow/ mean E' lateral and E' medial; *EF*, ejection fraction; *EDV*, end-diastolic volume; *LAV*, left atrial volume; *ESV*, end-systolic volume; *TDI s'*, tissue Doppler imaging s' at the lateral tricuspid annulus; *MAPSE*, mitral annular plane systolic excursion; *TAPSE*, tricuspid annular plane systolic excursion

Table 5.14. Multilevel linear mixed-effects models for systolic, diastolic and longitudinal function. Estimated marginal means (95% CI) for each trimester and group are given.

	1st Trimester 11-14 weeks			2nd Trimester 20-24 weeks			3rd Trimester 30-32 weeks		
	BMI 20-25 N=14	**BMI>30 N=64**	**P**	**BMI 20-25 N=14**	**BMI>30 N=64**	**P**	**BMI 20-25 N=14**	**BMI>30 N=64**	**P**
Systolic function									
EDV (mm)	83.9 (71.7-96.1)	100.2 (93.2-107.3)	**0.01**	85.5 (73.5-97.5)	101.2 (94.4-108.1)	**0.01**	87.6 (74.3-100.8)	102.8 (95.4-110.1)	**0.04**
EDV index (mm/BSA)	48.7 (43.6-53.9)	46.8 (43.9-49.8)	0.40	49.7 (44.6-54.7)	47.3 (44.5-50.2)	0.39	50.9 (45.6-56.1)	47.9 (45-50.9)	0.25
ESV (mm)	32.8 (26.7-38.9)	40.4 (36.8-44)	**0.01**	33.4 (26.8-40)	40.7 (37-44.4)	**0.04**	34.6 (27.8-41.4)	42.2 (38.4-46)	**0.03**
ESV index (mm/BSA)	19 (16.4-21.7)	18.8 (17.3-20.4)	0.80	19.4 (16.4-22.4)	19 (17.3-20.6)	0.83	20 (17.1-22.9)	19.7 (18.1-21.3)	0.88
EF (%)	61.7 (58.6-64.7)	59.9 (58.2-61.7)	0.16	60.8 (57.4-64.2)	59.5 (57.6-61.4)	0.47	60.7 (57.6-63.8)	58.4 (57.7-61.2)	0.46
TDI s' (cm)	14.4 (12.9-15.8)	13 (12.2-13.9)	0.14	15.1 (13.5-16.7)	13.7 (12.8-14.5)	0.05	14.4 (12.7-16.2)	14 (13.1-15)	0.57
Diastolic function									
E/A ratio	1.79 (1.52-2.12)	1.38 (1.25-1.42)	**0.04**	1.71 (1.38-1.98)	1.31 (1.21-1.49)	**0.01**	1.62 (1.43-1.82)	1.21 (1.11-1.72)	**<0.001**
E' lateral (m/s)	17.2 (15.1-19.2)	14.6 (13.4-15.7)	**0.01**	16 (14-18)	13.7 (12.6-14.8)	**0.02**	14.9 (12.1-15.8)	13.1 (12.1-14.2)	0.06
E' medial (m/s)	11.6 (10.3-12.9)	9.7 (8.9-10.4)	**0.01**	10.6 (9.1-12)	9.8 (9-10.6)	0.05	10 (8.6-11.3)	8.8 (8-9.6)	0.08
E/ E' ratio	6.3 (5.2-7.3)	7.1 (6.5-7.6)	0.24	6.6 (5.6-7.6)	7.4 (6.8-7.9)	**0.04**	7.1 (5.8-8.3)	7.5 (6.8-8.1)	0.16
LAV (ml)	53.6 (50.2-58.1)	60.8 (55.9-65.7)	**0.01**	57 (49.9-59.1)	64.2 (59.6-68.7)	**<0.01**	57.8 (49.7-63.9)	64.5 (59.4-69.6)	**0.03**
LAV index (ml/BSA)	31.6 (24.6-32.7)	31.5 (26.1-30.8)	0.79	33.5 (28.3-36.8)	32.0 (27.7-32.4)	0.41	34.4 (28-36.7)	32.3 (27.8-32.8)	0.42
Longitudinal function									
TAPSE (mm)	23.9 (21.6-26.2)	21.5 (20.2-22.8)	**0.03**	24.9 (22.2-27.6)	22.5 (21-24)	**<0.01**	24 (21.4-26.6)	21.1 (19.7-22.6)	0.06
MAPSE septal (mm)	14.5 (12.2-15.5)	13.9 (14-15.8)	0.39	13.9 (12-14.9)	13.6 (12.8-14.5)	0.84	13.9 (11.8-14.8)	12.6 (11.8-13.4)	0.63
MAPSE lateral (mm)	15.2 (13.3-17)	15.7 (14.6-16.9)	0.47	14.8 (11.7-15.8)	14.1 (14.5-16.7)	0.26	14.1 (12.2-16)	13.2 (12.9-15)	0.96

BSA, body surface area*; E/A ratio*, mitral inflow E-wave/A-wave filling; *E' lateral*, tissue Doppler imaging E prime measured at lateral mitral annulus; *E' medial*, tissue Doppler imaging E prime measured at medial mitral annulus; *E/E' ratio*, E-wave mitral inflow/ mean E' lateral and E' medial; *EF*, ejection fraction; *EDV*, end-diastolic volume; *LAV*, left atrial volume; *ESV*, end-systolic volume; *TDI s'*, tissue Doppler imaging s' at the lateral tricuspid annulus; *MAPSE*, mitral annular plane systolic excursion; TAPSE, tricuspid annular plane systolic excursion

In summary, we assessed systolic function with the end-diastolic volume (EDV), end-systolic volume (ESV), EF and tissue Doppler imaging (TDI) s' at the lateral tricuspid annulus. In both groups the EDV and ESV had a small upward trend and EF a slight downward trend with gestation but there was no significant difference. When comparing the groups, ESV and EDV were higher in the obese group however, there was no difference in the indexed value corrected for BSA and no difference in EF. TDI s' at the tricuspid lateral annulus did not change with the gestation in either group but was lower in the obese compared to the normal BMI group.

Diastolic indices, mitral inflow E-wave/A-wave (E/A) ratio and TDI E' at the lateral mitral annulus decreased with gestation (Table 5.12) but TDI E' at the medial mitral annulus, E/E' ratio and LA volume did not change with gestation. When comparing the groups, the E/A ratio and TDI E' at lateral and medial were higher and E/E' ratio lower in the obese compared to the normal BMI group (Table 5.13, Figure 5.8 and 5.9). The LA volume was also higher in the obese group but this did not persist after correction for BSA.

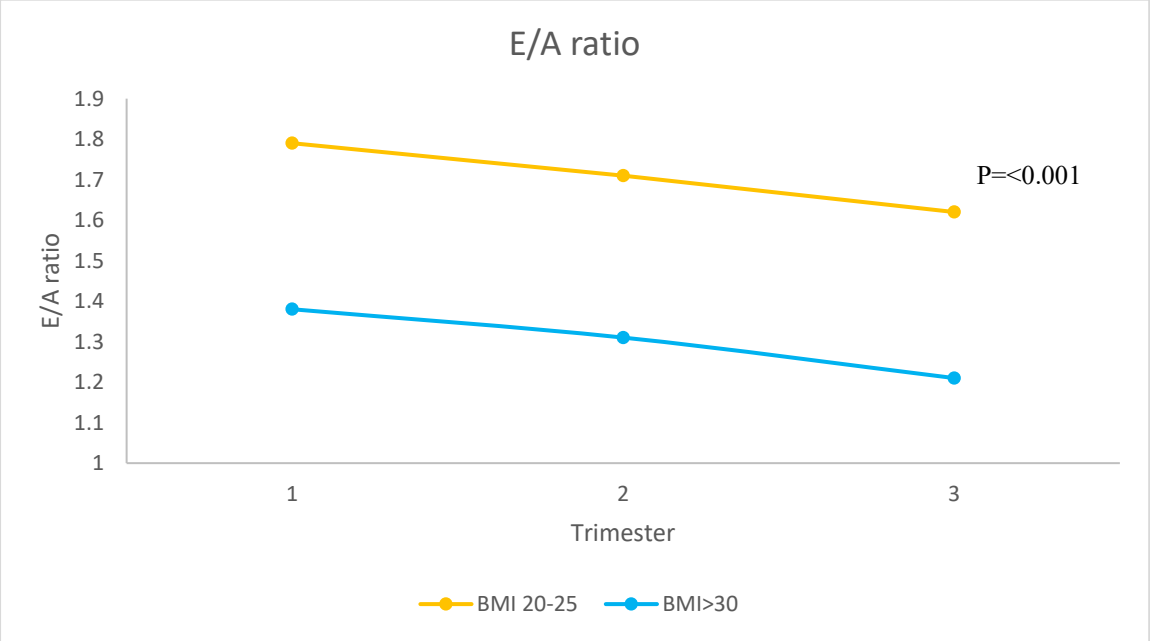


Figure 5.8. Mixed model analysis of E-wave/A-wave ratio across trimesters in both groups

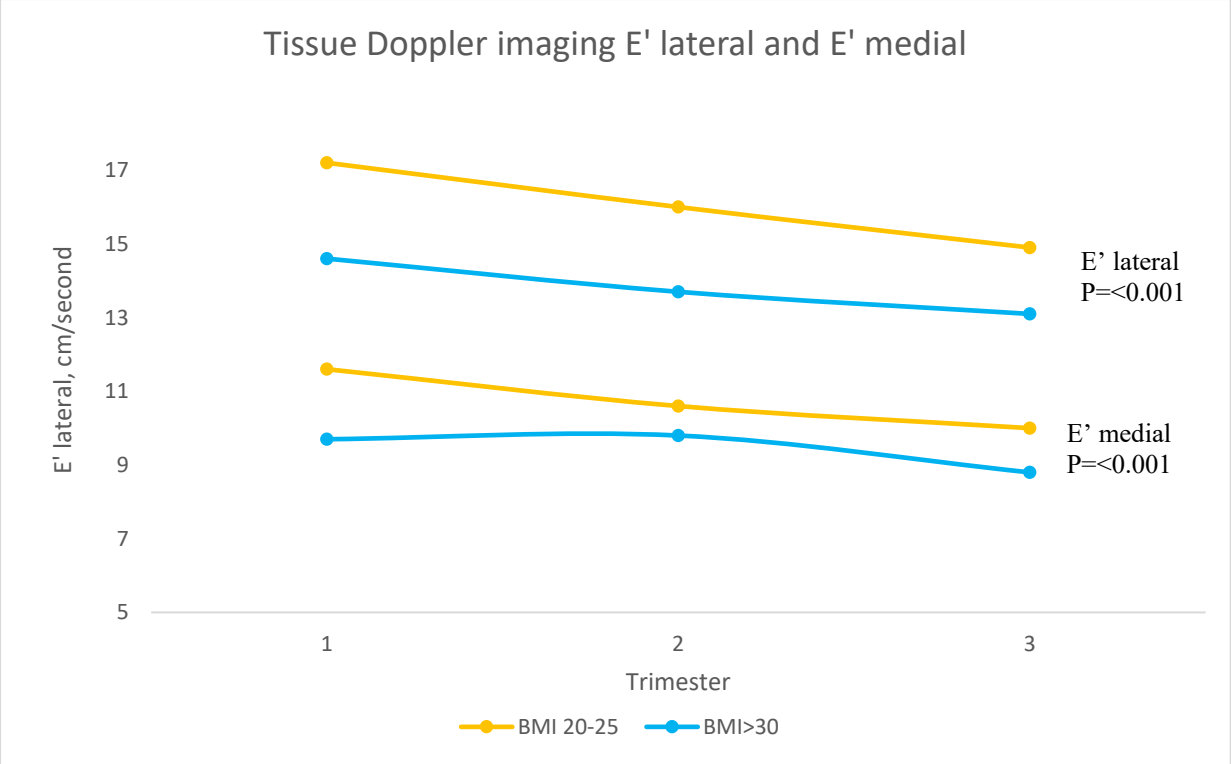


Figure 5.9. Mixed model analysis tissue Doppler imaging (TDI) E' at the lateral and medial mitral annulus across trimesters in both groups

Longitudinal function for the right heart was assessed by tricuspid annular plane systolic excursion (TAPSE) which did not change with gestation but was lower in the obese compared to the normal BMI group. For left longitudinal function, mitral annular plane systolic excursion (MAPSE) lateral and septal both reduced with gestation in the obese but not in the normal BMI group. When comparing the groups, there was no significant difference.

Birthweight

The birthweight percentiles in both groups examined are given in Table 5.1. We examined whether any of the maternal cardiovascular parameters including MAP, CO and TPR correlated with BW percentile in the whole cohort (Table 5.15 and Figures 5.10-5.11).

Table 5.15. Pearson's correlation (R) of cardiac output, total peripheral resistance and mean arterial pressure with birth weight percentile at each trimester in the whole cohort

	Trimester	R	P
CO	1	0.33	**<0.01**
	2	0.32	**<0.01**
	3	0.42	**<0.001**
TPR	1	-0.32	**<0.01**
	2	-0.22	0.05
	3	-0.42	**<0.001**
MAP	1	0.04	0.75
	2	0.09	0.44
	3	0.09	0.42

CO, cardiac output; *MAP*, mean arterial pressure; *TPR*, total peripheral resistance

In the whole cohort, we found a positive correlation between maternal CO in all trimesters and BW percentiles and a negative correlation between TPR, in the first and third trimesters, and BW (Figures 5.10 and 5.11).

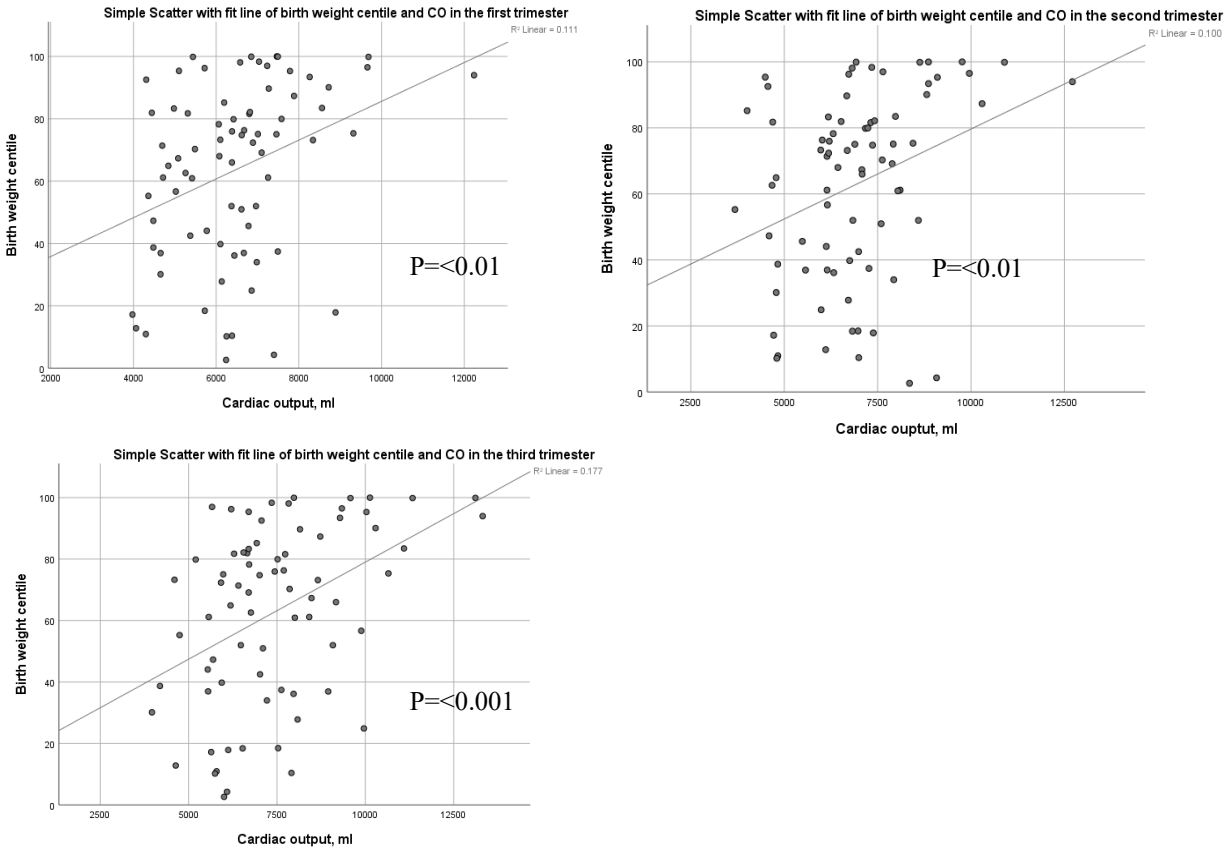


Figure 5.10. Correlation of cardiac output and birth weight percentile in the first, second and third trimester for the whole cohort.

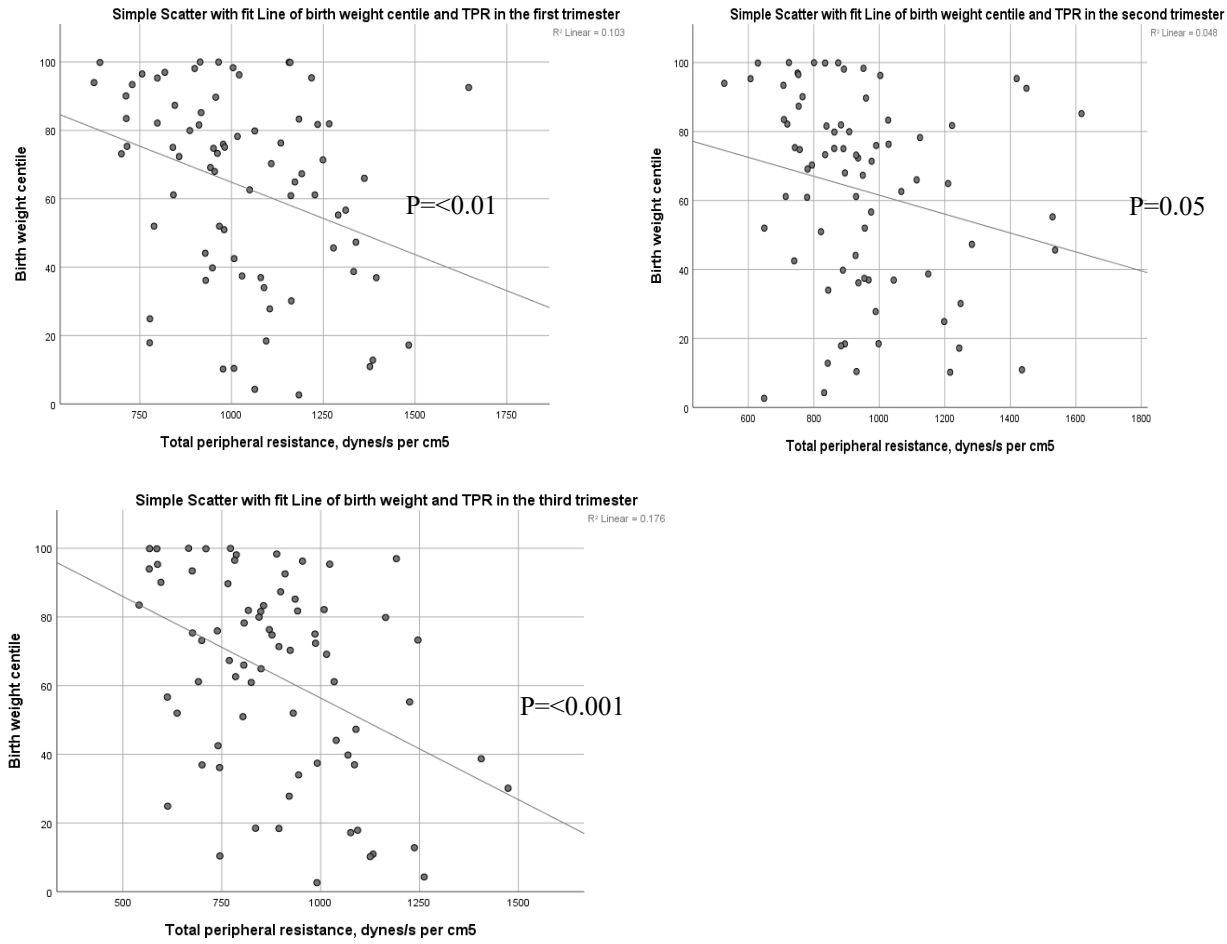


Figure 5.11. Correlation of total peripheral resistance and birth weight percentile in the first, second and third trimesters for the whole cohort

Discussion

This study has shown that, obese pregnant women have a different haemodynamic profile, altered cardiac geometry and impaired diastolic indices compared to pregnant women with a normal BMI. In particular, obese women have higher SBP, DBP, MAP, HR, SV and CO with lower TPR. Furthermore, obese women demonstrated higher LA diameter, IVS, LVEDD, 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 compared to the normal BMI group suggesting suboptimal cardiac geometry, haemodynamic and diastolic function.

Our haemodynamic findings in the obese group are consistent with literature of non-pregnant obese individuals. Obesity is associated with increased plasma volume expansion and CO due

to excess body mass, with a concomitant decrease in natriuresis. The raised CO leads to glomerular hyperfiltration and in turn raised distal tubular sodium delivery. Complex mechanisms lead to the upregulation of the renin-aldosterone-angiotensin system and stimulation of the sympathetic nervous system, which lead to increased sodium reabsorption, plasma volume expansion and arterial hypertension. (9, 10) 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 sympathetic activity. (6, 209) We note that between the second and third trimester the SV plateaued in the obese group whereas, there was a non-significant increase in the normal BMI women, this may represent a situation of volume overload in the third trimester in the former group as described in literature. (74) The higher HR and SV in the obese group resulted in higher CO. However, when corrected for BSA, the SVI was lower and CI non-significantly lower in the obese group in the third trimester (non-significance likely due to the increased HR). The lower SVI in the obese group the third trimester could again indicate an overstreched high volume system that is unable to keep up with the demands of the advancing gestation. (73) Furthermore, we have confirmed a higher maternal SBP, DBP and MAP in the obese pregnant women compared to the normal weight counterparts. (210)

Maternal TPR decreased with gestation in both groups, in accordance with normal pregnancy physiology, as peripheral vasodilation leads to a fall in systemic vascular resistance. (28) When comparing the groups, TPR 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 TPR is proportional to MAP and CO, an elevated CO, seen in our obese pregnant women, will result in TPR reduction. (13, 211)

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. (37, 166) 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 it has been reported that even in normal pregnancy a small proportion of women (5-6%) will have LV hypertrophy, defined by LV mass index>95g/m^2 and RWT>0.42. (37) Our findings are consistent with obesity physiology where there is a hyperdynamic circulation in order to cope with the metabolic demand of increased adipose tissue and fat-free mass, which leads to LV dilation, increased wall stress and compensatory

LV hypertrophy. Furthermore, hyperinsulinemia and hyperleptinemia could also be involved in the pathogenesis of LV hypertrophy seen in this population. (6, 212, 213)

As expected, we found that obese women had higher EDV and ESV, which did not persist after correction for BSA suggesting similar systolic function between the groups. Additionally, there was no difference in EF between the groups, this is consistent with obese individuals outside of pregnancy. (6, 214) Mitral annular plane systolic excursion assesses longitudinal function and gives an indication of systolic function. In normal pregnancy, lateral and septal MAPSE have been reported to be reduced at term. (37) We have found that obese women have a reduction in MAPSE between the second and third trimester, which could indicate early cardiac decompensation in this group.

There was a significant reduction in diastolic indices, E/A ratio and TDI E' at the lateral mitral annulus with gestation in accordance with literature published in normal pregnancy. It is thought that the physiological myocardial hypertrophy causes decreased LV compliance, leading to a reduction in early diastolic filling and a greater need for atrial contraction which results in an increased A-wave and reduced E/A ratio. (37, 215) 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 which again is in keeping with reported findings in obese individuals. (22, 216) Left ventricular hypertrophy leads to impaired relaxation and early filling abnormalities which are compensated by augmented atria1 contribution; these findings represent an early index of cardiac dysfunction when systolic performance is normal. (217)

Right heart function, as assessed by TDI s' and TAPSE, were lower in the obese compared to the normal BMI group in accordance with findings outside the setting of pregnancy suggesting suboptimal right heart function due to obesity. (218)

We found a correlation across gestation between haemodynamic parameters (CO and TPR) and BW, which is in agreement with other studies showing that pre-pregnancy, early pregnancy and third trimester CO and TPR are associated with BW, highlighting the importance of maternal cardiovascular function in maintaining a healthy pregnancy. (46, 58, 219)

The relationship between obesity and hypertension outside the setting and during the course of pregnancy is well documented. (8, 66) It has been reported that obese mothers are almost three

times more likely to develop gestational hypertension or PE compared to those with a normal BMI. This risk is dose dependant and doubles with each 5 to 7 unit increase in pre-pregnancy BMI (63) and it is almost five times more in morbidly obese women (BMI>50). (64, 220, 221) It is conceivable that maternal obesity induced insulin resistance is associated with a reduced cytotrophoblast migration and uterine spiral artery remodelling, which leads to placental hypoxia and ischemia, which in turn leads to the release of anti-angiogenic and inflammatory factors into the maternal circulation promoting endothelial dysfunction, reduction in nitric oxide production and an increase in oxidative stress, that results in the development of PE. (222) 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. (47, 222) In accordance with this notion, maternal hyperdynamic circulation with high CO and low resistance has been described prior to the onset as well as during the clinical phase of late PE. (55, 56, 223) In addition, a higher early pregnancy maternal BP increases the susceptibility of developing PE. (62, 224) With regard to cardiac geometry, it has been reported that 50% and 20% of pregnant women destinated to develop PE have evidence of cardiac remodelling, with higher RWT, and concentric hypertrophy, respectively. Additionally, diastolic function has been shown to be reduced prior to the onset of term and pre-term PE. (53, 55) We have found that obese pregnant women also share features of a hyperdynamic circulation with high BP and CO with low resistance, LV hypertrophy and reduced diastolic indices. Given the similarities between the cardiac profile of obese pregnant women and that of the pre-clinical phase of PE, it would be reasonable to assume that the maternal cardiovascular adaptation of these women may predisposed them to the development of hypertensive disorders during pregnancy.

Conclusions

In summary, we found that obese pregnant women have a different haemodynamic profile with higher BP, CO and lower TPR, compared to normal BMI pregnant women. In addition, obese women have altered cardiac geometry with a higher LV mass and prevalence of hypertrophy and suboptimal diastolic function. The haemodynamic indices, cardiac geometry and diastolic function in obesity all share features of the cardiovascular profile described in the pre-clinical phase of PE and this may make these women more vulnerable to the development of hypertension. Further studies are warranted to confirm that.

Chapter 6

Maternal cardiovascular indices and placental function in overweight/obese pregnant women

Abstract

Background: During pregnancy significant maternal cardiovascular changes are needed to support fetal growth and the competence of the maternal cardiovascular system may determine the quality of the placental and fetal circulation. There is evidence that haemodynamic indices are associated with placental function and birth weight in normal pregnancy. It has been shown that lower maternal cardiac output and higher resistance is associated with a higher uterine artery impedance; a key indicator of fetal growth restriction. Obesity is known to have several cardiovascular implications and in pregnancy there is an increased risk of developing hypertensive disease. Studies of obese pregnant women report altered hyperdynamic, systolic and diastolic function and it is thought this maladaptation may be linked to adverse outcomes in this population.

Objective: The aim of the current study was to investigate longitudinally the association between maternal cardiovascular function and placental function in overweight/obese pregnant women.

Methods: This was a prospective, observational, longitudinal study including 84 pregnant women with booking body mass index (BMI)>25. Participants were seen at three time points; 12-14, 20-24 and 30-32 weeks of pregnancy. At each visit blood pressure was measured and maternal cardiac function was assessed using trans-thoracic echocardiography. Pearson's correlation coefficient was used to evaluate the correlation between cardiac parameters and placental function (PAPP-A, β-hCG, uterine artery pulsatility index) and birth weight (BW).

Results: Maternal cardiac output and left atrial volume positively, and total peripheral resistance negatively correlated with BW percentile. Furthermore, in the first trimester, left

atrial volume negatively correlated with uterine artery pulsatility index and systolic blood pressure in the second trimester negatively correlated with PAPP-A.

Conclusions: The study has shown an association between maternal hemodynamic indices and placental function and birth weight in overweight and obese pregnant women. We support existing evidence of the importance of the maternal cardiovascular system in the pathogenesis of fetal outcomes.

Introduction

During pregnancy, several coordinated and regulated processes take place to enable successful fetal development. The formation and development of the placenta is one of these critical events. This organ plays an essential role in pregnancy including fetal nourishment and gaseous exchange.(225) The placenta, through implantation and development, modifies the uterine circulation from one of low flow and high resistance to one of high flow and low resistance; inadequate trophoblastic invasion predisposes to uteroplacental complications. (226) Doppler ultrasonography can be used in pregnancy to assess the feto-placental circulation, with the uterine artery doppler pulsatility index (PI) indicating vascular resistance on the maternal side of the placental circulation and the umbilical artery PI indicating the vascular resistance on the fetal side of the placenta. Doppler ultrasound of the uterine arteries gives indirect evidence of uterine blood flow changes in pregnancy. (227, 228)

Placental hormones, mainly secreted by the syncytiotrophoblasts in a highly regulated way, are vital for pregnancy establishment and maintenance. Beta human chorionic gonadotropin (β-hCG) mediated effects are essential for early pregnancy maintenance and pregnancy associated plasma protein (PAPP-A), along with insulin-like growth factors, is involved in invasion of the endometrium and regulation of fetal growth. (229) As these hormones are released into the maternal circulation, they can be targeted as biomarkers for the prediction of pregnancy complications; PAPP-A and β-hCG are efficient serum markers in first trimester screening for chromosomal abnormalities. (229, 230) In addition, there is evidence that low PAPP-A in the first trimester can also be associated with fetal growth restriction (FGR) and pre-eclampsia (PE). (231)

Normal pregnancy is associated with significant maternal cardiovascular and haemodynamic changes that are needed to support fetal growth. Systemic vasodilation leads to a reduction in

resistance and an increase in stroke volume (SV) and cardiac output (CO) ensuring optimal blood supply to the placenta and fetus. (28) Maternal haemodynamic function had become an area of interest in the pathophysiology of healthy and complicated pregnancy. In healthy pregnancy, it has been shown that maternal CO from preconception and early pregnancy can influence third trimester fetal growth and birth weight (BW). It is thought that a low maternal CO and high resistance state results in reduced placental perfusion. As the timing of the haemodynamic changes occur prior to the development of a functional placental unit at 12 weeks, it has been suggested that the maternal cardiovascular system, rather than primary placental dysfunction, is the origin of pregnancy complications. (59) The competence of maternal cardiovascular function may determine the quality of the placental and fetal circulation, which links maternal CO with changes in the maternal uterine and fetal umbilical doppler. (232) Lower maternal CO and higher peripheral vascular resistance (PVR) have been shown to be associated with a higher umbilical and uterine artery impedance; both are key indicators of fetal growth restriction. (232, 233) Tay et al. reported that uterine artery PI was higher in fetal growth restriction with or without pre-eclampsia (PE) but not in PE alone. They reported a negative relationship between CO and uterine and umbilical artery PI and a positive relationship between PVR and uterine and umbilical PI. (232) A recent large study of normal pregnancy in the third trimester found that placental function, assessed by placental growth factor and soluble fms-like tyrosine kinase 1, were non-lineally associated with CO and PVR. In addition, estimated fetal weight was positively and negatively associated with CO and PVR respectively. They concluded that although causal mechanisms could not be established, there is evidence of a significant relationship between maternal hemodynamic function and fetoplacental needs. (234) Further to this, a longitudinal study of left atrial (LA) volume index found that it successfully depicts cardiac adaptation to hemodynamic changes in pregnancy and an increase in LA volume index negatively correlated with uterine artery PI, reflecting a pronounced cardiac adaptation to increased blood volume in pregnancy. (235)

Obesity is known to have several cardiovascular implications outside of pregnancy with increased SV and heart rate (HR) leading to increased CO, changes in cardiac geometry and compromised diastolic and sometimes systolic function. (6) The cardiovascular adaptation to pregnancy in obese women is associated with increased blood pressure (BP), CO and left ventricle (LV) mass. Cardiac index (CI), the CO corrected for body surface area, has been reported as both high and low in obese pregnant women compared to normal BMI pregnant women. (72, 236) Obesity is associated with adverse pregnancy outcomes, notably

hypertensive disorders. Studies of obese pregnant women report a hyperdynamic circulation with high CO and low resistance with evidence of reduced diastolic and systolic function, compared to non-obese pregnant women. This maladaptation has been thought to be linked to adverse outcomes in this population.

With regard to placental function in obesity, a large study of 4212 women that found that the physiological reduction in uterine artery PI during gestation was significantly less in overweight and obese compared to normal weight women. They conclude that there may be reduced baseline compliance in the uterine vasculature leading to impaired remodelling and an inadequate reduction in the uterine artery PI, which may be related to an increased incidence of placenta-related diseases in this population. (237) A population based study of maternal characteristics found higher pre-pregnancy BMI was associated with higher third-trimester uterine artery RI. (238) Another longitudinal study reported that in the second and third trimesters, obese women with BMI ≥40 had higher mean uterine artery PI compared to normal weight women. (239) Conversely, a study at term found that normal weight, overweight and obese women have similar maternal and fetal blood flow parameters. However, there was a positive association between BMI and uterine artery RI. (240)

Studies of the maternal cardiovascular system and placental function in obese pregnant women are limited. A longitudinal study of cardiac performance in obese pregnant compared to normal BMI pregnant women, reported that in both groups there was significant decrease in uterine PI from the first to the third trimester, however, there was a smaller decrease in the obese group. In the whole cohort, CI measured in the first trimester negatively correlated uterine artery resistance index (RI) measured in the third trimester. Cardiac index and LV mass were independent predictors of upper quartile uterine artery RI in the third trimester. The authors concluded that a relationship exists between maternal cardiac adaptation and uterine arteries flow pattern and that lower CI can affect spiral artery remodelling in early pregnancy, which may lead to placental hypoperfusion in later pregnancy in obese women. (236)

As described, there is evidence that haemodynamic indices are associated with placental function and BW in normal pregnancy. (234) Furthermore, overweight and obese pregnant women demonstrate a lesser reduction in uterine artery PI with gestation, compared to normal weight pregnant women. (237) Only one study has considered the association of maternal haemodynamic indices with placental function but the results were reported for the whole

population rather than just the obese group. (236) The aim of the current study was to investigate longitudinally the association of maternal cardiovascular function with placental function and BW, as assessed by measurements of PAPP-A, β-hCG, uterine artery PI and BW percentile, in overweight/obese pregnant women.

Hypothesis

Maternal cardiovascular function is associated with placental function and BW in overweight/obese pregnant women.

Aims

1. Investigate the association of maternal cardiovascular function with placental function, as assessed by first trimester PAPP-A, β-hCG levels and uterine artery doppler assessment in overweight/obese pregnant women.
2. Investigate the association of maternal cardiovascular function with BW percentile in overweight/obese pregnant women.

Methods

This was a prospective, observational, longitudinal study. Pregnant women were recruited from April 2018 to June 2020 at Chelsea & Westminster Hospital, London, UK. Participants were identified through a booking-perinatal database (CIMIS), as previously described, and low risk women with a booking BMI >25 and singleton pregnancy were approached and recruited. Participants were seen at three time points during their pregnancy, 12-14, 20-24 and 30-32 weeks and women that attended at least two out of three research visits were included in this study. Maternal characteristics, including age, parity, race, smoking status, method of conception and medication history were recorded in the research database. Maternal weight, height and manual BP were calculated and recorded. PAPP-A and β-hCG were measured as part of the first trimester combined screening test (nuchal translucency, PAPP-A and β-hCG) for chromosomal abnormalities and was recorded as multiples of median (MoM). Transvaginal ultrasound scans were performed at each visit using a 5-9 MHz probe (Voluson E8 GE Healthcare system, USA). Pulsed wave Doppler was used to assess the utero-placental circulation. Three consecutive waveforms of the left and right uterine arteries were obtained

and the mean of two readings of the PI was recorded. (126) At each visit, the maternal cardiovascular function was assessed by 2D and Doppler trans-thoracic echocardiography using the iE33 Ultrasound System (Philips Ultrasound, USA) equipped with a S5-1 transducer (frequency 1-5MHz). The echocardiography methodology is described in further detail in Chapter 2. Cardiovascular parameters assessed included systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), CO, stroke volume (SV), total peripheral resistance (TPR), left atria (LA) volume, mitral inflow velocity E-wave/A-wave (E/A) ratio and ejection fraction (EF).

Information on pregnancy outcomes were obtained from the Hospital's perinatal database. Development of gestational diabetes (GDM) and hypertensive disorders of pregnancy were defined as previously described (Chapter 2). Birth weight percentiles were calculated as previously described (Chapter 2).

Statistical analysis

Pearson's correlation coefficient (R) was used to evaluate the correlation between cardiac parameters and PAPP-A, β-hCG, uterine artery PI and BW percentile. Regression analysis was used to assess whether correlations remained significant after consideration of the influence of maternal characteristics including gestation, maternal age, race and development of GDM.

Results

The study included 84 pregnant women with booking BMI >25 and the maternal characteristics of the study population are given in Table 6.1.

Table 6.1. Demographic characteristics and pregnancy outcomes of the study participants.

Variable	**BMI>25 N=84**
Age (years)	33.3 (4.8)
Racial group	
White, n (%)	66 (78.6)
Other, n (%)	18 (21.4)
Body mass index at booking (kg/m^2)	35.5 (7.0)
Parity	

Nulliparous, n (%)	41 (48.8)
Parous, n (%)	43 (51.2)
Conception	
Spontaneous, n (%)	75 (89.2)
Assisted reproductive technology, n (%)	9 (10.7)
Smoking	
No, n (%)	81 (96.4)
Yes, n (%)	3 (3.6)
Hypertensive disorders of pregnancy	
No, n (%)	77 (91.7)
Yes, n (%)	7 (8.3)
Gestational diabetes mellitus	
No, n (%)	70 (83.3)
Yes, n (%)	14 (16.7)
Mode of delivery	
Spontaneous vaginal delivery, n (%)	39 (46.4)
Operative vaginal delivery, n (%)	10 (11.9)
Caesarean section, n (%)	35 (41.7)
Gestational age at delivery (weeks)	38.9 (1.6)
Birth weight (gr)	3480 (3120-3770)
Birthweight percentiles (%)	69.1 (37.4-85.2)

Data are expressed as mean (standard deviation), median (interquartile range) or n (%).

Mean uterine artery PI decreased with gestation (Table 6.2) however, there was no correlation between BMI or weight and uterine artery PI (Table 6.3).

Table 6.2. PAPP-A, β-hCG and mean uterine artery pulsatility index, at each trimester in overweight and obese pregnant women.

	BMI25 **N=84**
PAPP-A (MoM)	0.95 (0.61-1.44)
β-hCG (MoM)	0.99 (0.76-1.71)
Mean UtAPI-T1	1.58 (1.33-1.91)
Mean UtAPI-T2	1.04 (0.83-1.15)
Mean UtAPI-T3	0.81 (0.71-0.91)
UtAPI T1-T2 Mean Decrease % Mean Decrease	 0.55 (0.39-0.81) -37.55(-46.03-(-24.96))
UtAPI T2-T3 Mean Decrease % Mean Decrease	 0.21 (0.11-0.36) -18.63(-29.85-(-10.55))
UtAPI T1-T3 Mean Decrease % Mean Decrease	 0.795 (0.55-1.08) -47.31(-57.57-(-39.09))

Data are expressed as median (interquartile range), *β-hCG*, beta human chorionic gonadotropin**,** *PAPP-A (MoM)*, plasma protein A (multiples of median), *UtAPI*, uterine artery pulsatility index, *T1-T2*, first trimester minus second trimester, *T2-T3*, second trimester minus third trimester, *T1-T3*, first trimester minus third trimester

Table 6.3. Pearson's corelation (R) of BMI and weight with mean uterine artery pulsatility index at each trimester

	BMI		Weight (kg)	
	R	P	R	P
UtAPI-T1	-0.01	0.91	0.03	0.98
UtAPI-T2	0.09	0.36	0.11	0.33
UtAPI-T3	0.12	0.27	0.07	0.57

UtAPI, uterine artery pulsatility index, *T1*, first trimester, *T2*, second trimester, *T3*, third trimester

We next investigated the association of maternal haemodynamic parameters and placental function/ BW percentile (Table 6.4). We found that first and second trimester SBP negatively correlated with PAPP-A and the first trimester HR positively correlated with BW percentile.

Table 6.4. Pearson's correlation of maternal blood pressure and heart rate with PAPP-A, β-hCG uterine artery PI and BW percentile at each trimester, in overweight/obese pregnant women.

	BW percentile		PAPPA (MoM)		β-hCG (MoM)		Mean UtAPI-T1		Mean UtAPI-T2		Mean UtAPI-T3	
	R	P	R	P	R	P	R	P	R	P	R	P
Log_{10} SBP-T1	0.10	0.42	-0.27	**0.02**	-0.07	0.54	-0.09	0.42	-0.02	0.88	-0.19	0.10
Log_{10} SBP-T2	0.10	0.42	-0.26	**0.02**	-0.08	0.54	-0.09	0.42	-0.02	0.88	-0.19	0.10
Log_{10} SBP-T3	0.05	0.67	-0.22	0.07	-0.03	0.791	-0.11	0.33	-0.16	0.18	-0.07	0.53
Log_{10} DBP-T1	0.03	0.82	0.03	0.83	0.15	0.199	-0.05	0.64	0.02	0.89	-0.08	0.50
Log_{10} DBP-T2	-0.09	0.48	-0.06	0.60	0.11	0.351	-0.08	0.49	-0.05	0.68	-0.15	0.19
Log_{10} DBP-T3	-0.06	0.64	-0.09	0.46	0.08	0.511	-0.07	0.57	-0.10	0.37	-0.21	0.07
Log_{10}HR-T1	0.23	**0.04**	-0.14	0.23	-0.01	0.918	0.04	0.74	-0.08	0.48	0.12	0.30
Log_{10}HR-T2	0.20	0.08	-0.13	0.25	-0.14	0.237	0.05	0.64	-0.13	0.23	0.11	0.33
Log_{10}HR-T3	0.17	0.14	-0.08	0.51	-0.09	0.456	0.01	0.99	-0.16	0.16	-0.06	0.59

SBP, systolic blood pressure, *DBP*, diastolic blood pressure, *HR*, heart rate, *T1*, first trimester, *T2*, second trimester, *T3,* third trimester, *BW*, birth weight percentile, *β-hCG*, beta human chorionic gonadotropin**,** *PAPP-A (MoM)*, plasma protein A (multiples of median), *UtAPI*, uterine artery pulsatility index

We investigated the association between maternal cardiovascular parameters and placental function/ BW percentile (Table 6.5) and found that in all trimesters, CO positively and TPR negatively correlated with BW percentile. Left atrial volume in the first and second trimester positively correlated with BW percentile and negatively correlated with the first trimester mean uterine artery PI.

Table 6.5. Pearson's correlation of cardiac output, stroke volume, total peripheral resistance and left atrial volume with PAPP-A, β-hCG, uterine artery pulsatility index and birth weight percentile at each trimester in overweight/obese pregnant women.

	BW percentile		PAPP-A (MoM)		β-hcg (MoM)		Mean UtAPI-1		Mean UtAPI-2		Mean UtAPI-3	
	R	P	R	P	R	P	R	P	R	P	R	P
Log_{10} CO-T1	0.29	**0.01**	-0.09	0.45	0.16	0.18	-0.02	0.85	-0.06	0.63	-0.06	0.61
Log_{10} CO-T2	0.29	**0.01**	-0.12	0.30	0.04	0.74	0.01	1.00	-0.12	0.30	-0.05	0.67
Log_{10} CO-T3	0.36	**<0.01**	-0.03	0.80	-0.02	0.89	0.02	0.88	-0.12	0.30	0.06	0.60

Log_{10} TPR-T1	-0.31	**0.01**	0.08	0.52	-0.12	0.31	-0.02	0.86	0.05	0.68	0.01	0.99
Log_{10} TPR-T2	-0.30	**0.01**	0.05	0.69	-0.03	0.82	-0.04	0.73	0.10	0.36	-0.03	0.78
Log_{10} TPR-T3	-0.38	**<0.01**	-0.03	0.79	0.02	0.88	-0.06	0.63	0.06	0.62	-0.13	0.28
Log_{10} SV- T1	0.17	0.12	-0.01	0.96	0.18	0.11	-0.05	0.66	-0.01	0.94	-0.16	0.19
Log_{10} SV-T2	0.19	0.09	-0.05	0.69	0.12	0.28	-0.03	0.78	-0.05	0.69	-0.12	0.30
Log_{10} SV-T3	0.32	**<0.01**	0.02	0.90	0.03	0.78	0.02	0.86	-0.04	0.76	0.12	0.32
Log_{10}LAV-T1	0.29	**0.02**	0.07	0.55	0.13	0.29	-0.28	**0.01**	-0.02	0.85	-0.11	0.39
Log_{10}LAV-T2	0.30	**0.01**	0.00	1.00	0.2	0.09	-0.14	0.22	-0.02	0.85	-0.07	0.55
Log_{10}LAV-T3	-0.02	0.85	-0.07	0.55	0.18	0.15	0.15	0.20	0.02	0.88	0.00	0.99

CO, cardiac output*, TPR,* total peripheral resistance*, SV,* stroke volume*, LAV,* left atrial volume*, T1*, first trimester, *T2*, second trimester, *T3,* third trimester, *BW,* birth weight percentile, *β-hCG*, beta human chorionic gonadotropin**,** *PAPP-A (MoM)*, plasma associated placental protein A (multiples of median), *UtAPI*, uterine artery pulsatility index.

We assessed the correlation of maternal systolic/diastolic function (EF and E/A ratio) with placental function (Table 6.6). In particular, second trimester ejection fraction inversely correlated with mean uterine artery PI in the 3rd trimester.

Table 6.6. Pearson's corelation of left ventricle ejection fraction and E-wave/A-wave ratio with PAPP-A, β-hCG, uterine artery pulsatility index and birth weight percentile at each trimester in overweight/obese pregnant women

	BW percentile		PAPP-A (MoM)		β-hCG (MoM)		Mean UtAPI-T1		Mean UtAPI-T2		Mean UtAPI-T3	
	R	P	R	P	R	P	R	P	R	P	R	P
LVEF (%)-T1	-0.03	0.78	0.05	0.70	0.06	0.60	-0.12	0.31	0.01	1.00	-0.17	0.16
LVEF (%)-T2	-0.16	0.05	0.05	0.68	-0.04	0.73	-0.01	0.91	0.01	0.97	-0.29	**0.01**
LVEF (%)-T3	-0.16	0.16	0.10	0.40	0.04	0.73	-0.06	0.61	-0.01	0.94	-0.07	0.55
E/A-T1	-0.16	0.16	0.10	0.39	0.16	0.17	0.02	0.88	-0.06	0.62	-0.10	0.42
E/A-T2	-0.05	0.69	0.04	0.74	0.08	0.50	0.15	0.18	0.23	0.05	0.01	1.00
E/A-T3	-0.17	0.13	0.14	0.23	0.23	0.06	0.05	0.68	0.11	0.34	0.10	0.39

EF, ejection fraction, *E/A ratio,* E-wave/A-wave ratio*, T1*, first trimester, *T2*, second trimester, *T3,* third trimester, *BW,* birth weight percentile*, β-hCG*, beta human chorionic gonadotropin**,** *PAPP-A (MoM)*, plasma associated placental protein A (multiples of the median), *UtAPI*, uterine artery pulsatility index.

Regression analysis was used to assess whether correlations remained significant after the influence of maternal characteristics, including gestation at assessment, maternal age, race and development of GDM (Tables 6.7 and 6.8) After adjustment for maternal characteristics, CO (all trimesters) and LA volume (first and second trimesters) remained positively and TPR (all trimesters) remained negatively associated with BW percentile respectively (Figures 6.1-6.2). Left atrial volume in the first trimester remained positively correlated with uterine artery PI and SBP in the second trimester negatively correlated with PAPP-A (Table 6.7 and 6.8).

Table 6.7. Linear regression model of cardiac output, total peripheral resistance and left atrial volume with birth weight percentile, after adjustment for gestation, maternal age, race and development of gestational diabetes

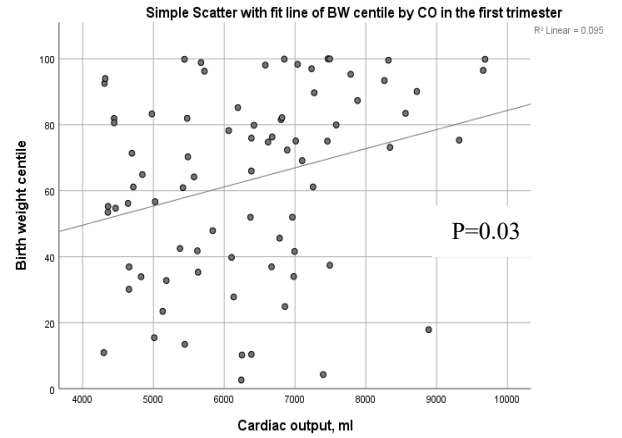
	BW percentile	
	R	P
Log_{10} CO-T1	0.39	**0.03**
Log_{10} CO-T2	0.42	**0.01**
Log_{10} CO-T3	0.46	**<0.01**
Log_{10} TPR-T1	-0.42	**0.01**
Log_{10} TPR-T2	-0.44	**0.01**
Log_{10} TPR-T3	-0.47	**<0.01**
Log_{10}LAV-T1	0.41	**0.02**
Log_{10}LAV-T2	0.43	**0.01**
Log_{10}LAV-T3	0.3	0.31

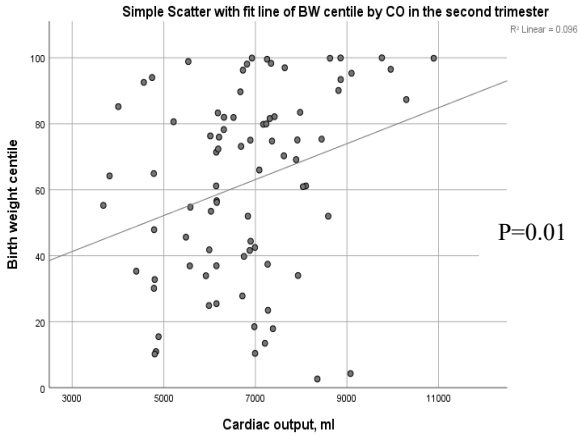
CO, cardiac output*, TPR,* total peripheral resistance*, LAV,* left atrial volume*, T1*, first trimester, *T2*, second trimester, *T3,* third trimester, *BW,* birth weight

Table 6.8. Linear regression model of systolic blood pressure and PAPP-A, after adjustment for gestation, maternal age, race and development of gestational diabetes

	PAAP-A	
	R	P
Log_{10}SBP-1	0.38	0.06
Log_{10}SBP-2	-0.21	**0.03**
Log_{10}SBP-3	0.34	0.14

SBP, systolic blood pressure, *PAPP-A (MoM)*, plasma associated placental protein A (multiples of the median)





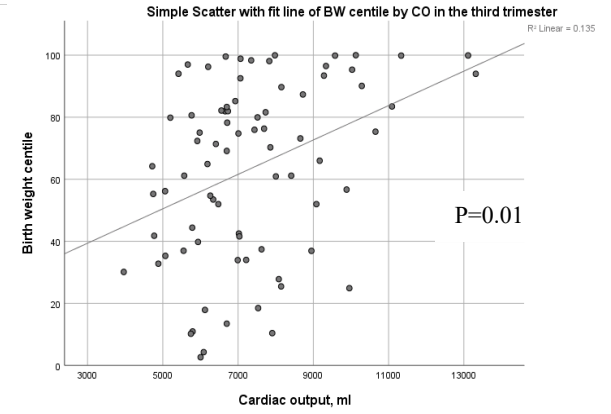
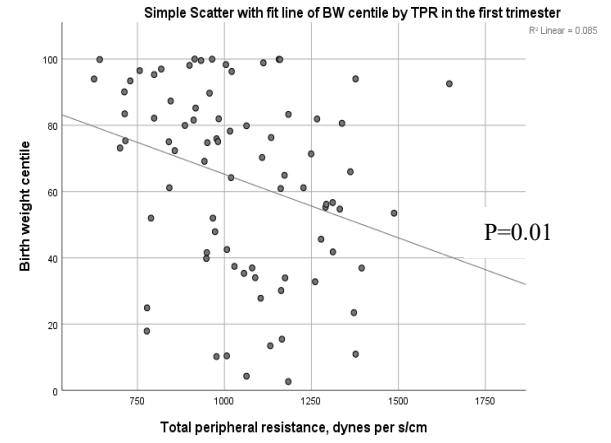
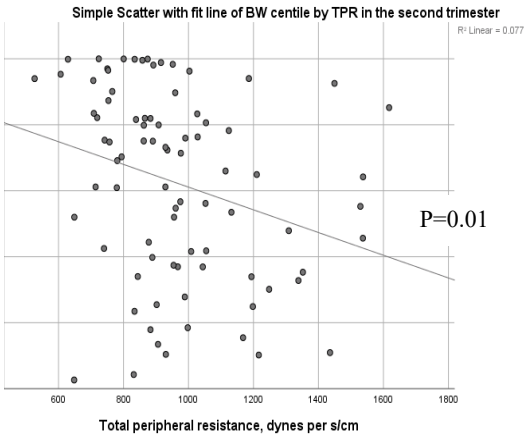


Figure 6.1. Correlation of cardiac output and birth weight percentile in each trimester





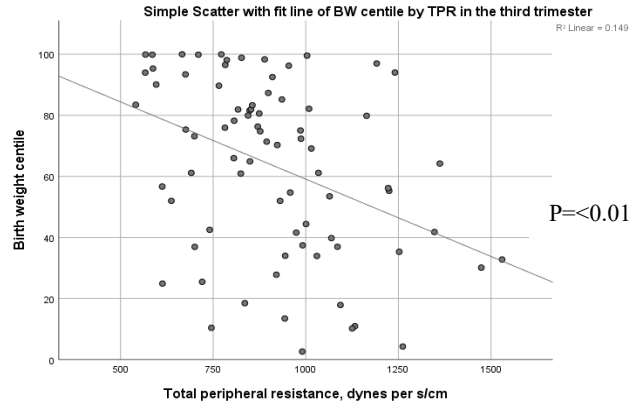


Figure 6.2. Correlation of total peripheral resistance and birth weight percentile in each trimester

Discussion

The study has shown that maternal CO and LA volume positively and TPR negatively correlated with BW percentile. Furthermore, in the first trimester, LA volume negatively correlated with uterine artery PI and SBP in the second trimester negatively correlated with PAPP-A. These correlations remained significant even after adjustment for maternal characteristics. Our results show an association between maternal hemodynamic indices and placental function and BW in overweight and obese pregnant women.

In keeping with expected physiological changes, uterine artery PI decreased with gestation between the first and second trimester (37.6%) and between the second and third trimester (18.6%). Our findings are similar to those reported in overweight/obese pregnant women, second to third trimester decrease of 21.3% in overweight/obese vs 25.7% in normal BMI pregnant women. (237) It is also reported that BMI is positively associated with uterine artery RI. (238, 240) In our study we did not find a correlation between BMI and uterine artery PI; this could have been due to the smaller sample size.

When correlating haemodynamic indices to placental function, we found that in all trimesters, maternal CO positively and TPR negatively correlated with BW percentile. In addition, LA volume in the first and second trimester also positively correlated with BW percentile and second trimester SBP negatively correlated with PAPP-A. Studies of normal BMI pregnant women also report similar association indicating that maternal cardiovascular changes may play an important role in determining fetal growth and BW. (58, 59, 234, 241, 242) We report that this correlation can be extended to overweight/obese pregnant women. Left atrial volume in the first trimester negatively correlated with mean uterine artery PI, this is similar to a study in normal weight pregnant women that reported a similar negative corelation between LA volume and uterine artery PI and concluded that a lower resistance in the uterine arteries is a reflection of a more pronounced cardiac adaptation to increased blood volume depicted by the increase in the LA volume. (235)

In recent years it has been considered that PE and FGR may have a cardiovascular rather than placental origin. (47, 53) Both cardiovascular disease and PE have shared risk factors including advanced maternal age, weight, ethnicity and development of diabetes. It is thought that placental oxidative stress or hypoxia is associated with the relative balance of cardiovascular functional reserve and the cardiovascular volume/resistance load of pregnancy. (47) Studies of

PE have reported altered haemodynamic indices with high CO and low resistance both before and at the clinical onset of PE. (55, 56, 223) In addition, it has been shown that women destinated to develop PE have abnormal cardiac geometry and diastolic dysfunction in the pre-clinical phase. (53) Furthermore, there is an increased risk of cardiovascular disease long-term despite the general notion that delivery is the 'cure' for PE and 50% of women will continue to have persistent hypertension.(50, 243)

Early onset PE is more commonly associated with FGR and characterised by low CO and high TPR, whereas late PE is associated with high CO and low TPR. (46, 55) Raised uterine artery resistance is reported in early PE corresponding with increased growth restriction, whereas, in late onset PE, BW is normal or even increased with no increase in uterine artery resistance. (244, 245) Our findings of uterine artery PI in the overweight/obese population in the three trimesters of pregnancy were similar to that of normal references ranges suggesting that placental function is not different in our population and that late PE may be due to maternal cardiovascular compromise rather than placental dysfunction. (246)

Conclusion

We build on existing evidence of a direct link between haemodynamic function (SBP, CO, TPR and LA volume) and placenta-dependent indices and have shown that this relationship extends to overweight/obese pregnant women.

Chapter 7

Effect of post-bariatric maternal weight loss and surgery to conception interval on perinatal outcomes of nulliparous women

Abstract

Background: Bariatric surgery is associated with an increased risk of delivering a small neonate. The role of maternal weight loss and surgery to conception interval is unclear.

Objectives: To investigate the effect of maternal weight loss, as a result of bariatric surgery, and surgery to conception interval on fetal growth and birthweight

Methods: This was a prospective study of nulliparous women with previous bariatric surgery. The type of surgery, time and pre-surgery weight was recorded, surgery-to-conception interval was calculated as the time between surgery and conception, defined as the fourteenth day of the pregnancy dated by first trimester ultrasound scan. Maternal weight was measured in the first trimester and maternal weight change between pre-surgery and the first trimester of pregnancy was defined as total weight loss. Fetal ultrasound scans were performed twice; 30-32 and 35-37 weeks gestation and estimated fetal weight was calculated. Fetal growth rate was calculated as the ratio of EFW increase (gr) between 30-32 and 35-37 weeks divided by the time interval (days) between the two examinations. Birth weight was recorded.

Results: The study included 54 pregnant women; 26 with a restrictive procedure (gastric band or vertical sleeve gastrectomy) and 28 with a gastric bypass. Surgery to conception interval was not a significant predictor of the offspring's growth, however, maternal total weight loss was a significant predictor of fetal growth rate and predictor of birth weight, which remained after adjustment for confounders.

Conclusions: Maternal weight loss, as a result of bariatric surgery, has an inverse correlation with fetal growth rate and birth weight.

Introduction

The rates of obesity are rising worldwide and in the UK, the latest NHS statistics report 60% of women overweight and 29% obese. (247) Many of these women are of reproductive age. The adverse effects of obesity are well known, notably this increased risk of developing metabolic syndrome, diabetes, cardiovascular disease and death. (248) Lifestyle changes and pharmacological treatment has been predominantly unsuccessful in achieving and maintaining normal weight. (249) Conversely, bariatric surgery is proven to be the most successful treatment for sustainable weight loss and the number of procedures performed is increasing yearly. (79) Considering the beneficial effects of weight loss on health as well as fertility, it is unsurprising the number of women entering pregnancy having had a previous bariatric surgery is increasing. (250) Large studies show that that bariatric surgery improves pregnancy outcomes by reducing the rate of gestational diabetes (GDM), pre-eclampsia (PE) and delivery of large-for-gestational age (LGA) neonates. However, surgery is also associated with an increased rate of small-for-gestational age (SGA) neonates. (111, 114) Several factors may determine the impact of bariatric surgery on pregnancy outcomes, but many of them have not been sufficiently investigated. It is recommended that pregnancy should be avoided in the first 12-24 months following bariatric surgery due to the theoretical harmful effect of maternal nutritional deficiencies on the fetal development (251) but a number of retrospective studies investigating the effect of surgery-to-conception interval on perinatal outcomes have shown no clear correlation between timing and pregnancy outcomes, including birthweight (BW). (252-254) Nevertheless, none of the previous studies have assessed the correlation of the amount of weight loss after bariatric surgery, with pregnancy outcomes. Furthermore, although most of published studies based their investigations on data from the first pregnancy following bariatric surgery, they all included both nulliparous and parous women, without taking into consideration the previous obstetric history. Parity is predictor of pregnancy outcomes and known to influence the risk of developing PE, GDM, preterm delivery, LGA or SGA neonate and as a result, lack of adjustment for previous obstetric history may have masked some of the effects of the surgery on pregnancy outcomes. (255-259)

The aim of this study was to investigate the effect of maternal weight loss and surgery to conception interval on the pregnancy outcome, in particular fetal growth and BW, in nulliparous women with previous bariatric surgery.

Methods

This was a prospective, observational, longitudinal study. Pregnant women were recruited from May 2015 to April 2020 at Chelsea & Westminster Hospital, London, UK. Participants were identified through a booking-perinatal database (CIMIS). Following the 1st trimester scan, participants were approached by members of the research team and recruited if they were nulliparous women with singleton pregnancies and had previous bariatric surgery. Maternal demographics were obtained at the first research visit and recorded in our database. Information on the type, time of the bariatric surgery and weight prior to the procedure was self-reported. Assessment of maternal weight change between pre-surgery and first trimester of pregnancy was defined as percent total weight loss (change) (%TWL) = (pre-surgery weight- early pregnancy weight)/pre-surgery weight. Surgery-to-conception interval was calculated as the time (in months) between surgery and conception which was defined as the fourteenth day of pregnancy, as determined by the first trimester ultrasound scan. Women recruited prior to December 2017 underwent a 75gr 2h oral glucose tolerance tests (OGTT) at 27-30 weeks of gestation and GDM was defined according to NICE guidelines of fasting plasma glucose level ≥5.6mmol/L and/or a 2-hour plasma glucose level of ≥7.8mmol/L. (128) Following publications that OGTT may not be reliable for GDM diagnosis in women with previous gastric bypass surgery, women recruited after December 2017 had capillary blood glucose monitoring for two weeks as a diagnostic test for GDM. (127) Fetal ultrasound examinations were performed twice at 30-32 and 35-37 weeks' gestation and estimated fetal weight (EFW) was calculated based on measurements of fetal head circumference (HC), abdominal circumference (AC) and femur length (FL). (260) Fetal growth rate was calculated as the ratio of EFW increase (in gr) between 30-32 and 35-37 weeks divided by the time interval (in days) between the two examinations. Information on pregnancy outcomes was obtained from the Hospital's perinatal database. Birth weight (BW) percentiles were calculated using fetal weight and gestation according to the Fetal Medicine Foundation. (131) Small-for-gestational age (SGA) was defined as BW less than the 10th percentile for the gestation. Large-for-gestational age (LGA) was defined as BW more than the 90th percentile for the gestation.

Statistics

After assessment of normality data were expressed as mean (standard deviation) or as median (interquartile range) for normally and not normally distributed data respectively and as a

percentage for categorical variables. Non-parametric data was made Gaussian after $\log_{10}$ transformation. Pearson's correlation coefficient (R) was used to evaluate the correlation between variables and variables with a univariate test p value of 0.15 were entered into a multiple regression analysis model.

Results

The study included 54 nulliparous women with a previous bariatric surgery; 26 with a restrictive procedure (gastric band or vertical sleeve gastrectomy) and 28 with a previous gastric bypass. The maternal demographics and pregnancy outcomes of the study participants are given in Table 7.1.

Table 7.1. Maternal demographic characteristics and pregnancy outcomes of the study participants

Parameters	**All** **n=54**
Maternal age (years)	33.31 (5.8)
Racial group	
White, n (%)	46 (85.2)
Other, n (%)	8 (14.8)
Smoking	
No, n(%)	51 (94.4)
Yes, n(%)	3 (5.6)
Method of conception	
Spontaneous, n(%)	48 (88.9)
Assisted Reproductive Technology, n(%)	6 (11.1)
Type of bariatric surgery	
Gastric band, n (%)	11 (20.4)
Vertical sleeve gastrectomy, n (%)	15 (27.8)
Gastric bypass, n (%)	28 (51.8)
Pre-surgery weight (kg)	126.3 (25.0)
Pre-surgery BMI (kg/m^2)	46.6 (8.3)
Surgery to early pregnancy total weight loss (kg)	35.4 (20.7)

Surgery to early pregnancy total weight loss (%)	26.8 (14.2)
Body mass index reduction (kg/m^2)	13.3 (7.4)
Body mass index reduction (%)	27.5 (13.4)
Surgery to conception time interval (months)	49.9 (31.4)
Booking weight (kg)	90.5 (18.8)
Booking body mass index (kg/m^2)	33.1 (6.3)
Estimated fetal weight at 30-32 weeks (gr)	1745.6 (236.6)
Estimated fetal weight at 35-37 weeks (gr)	2651.4 (348.1) (n=51)
Fetal growth rate (gr/day)	28.8 (6.5) (n=51)
Birthweight (gr)	3070.9 (564.2)
Birthweight (percentile)	34.1 (32.3)
Gestational age at delivery (weeks)	39.1 (1.4)
Small for gestational age, n(%)	18 (33.3)
Large for gestational age, n(%)	5 (9.3)
Estimated fetal weight at 30-32 weeks (gr)	1745.6 (236.6)
Mode of delivery	
Vaginal, n(%)	29 (53.7)
Caesarean section, n(%)	25 (46.3)
GDM	
No, n(%)	43 (79.6)
Yes, n(%)	11 (20.4)
Hypertensive disorders	
No, n(%)	51 (94.5)
Yes, n(%)	3 (5.6)

Compared to women with a previous restrictive procedure, those with a gastric bypass had higher pre-surgery weight [117.5 (27.0) kg vs 134.2 (20.5) kg; p=0.01], pre-surgery BMI [43.9 (8.2) kg/m^2 vs 49.0 (7.7) kg/m^2; p=0.02), pre-surgery to early pregnancy weight loss [20.9 (15.0)% vs 32.1 (11.4)%; p=0.003) and pre-surgery to early pregnancy BMI reduction [22.1 (13.7)% vs 32.2 (11.3)%; p=0.005]. Most of the women conceived spontaneously and only five women conceived within 12 months of the surgery.

In the whole group of 54 women, we aimed to identify which of the surgery, maternal demographic and pregnancy characteristics could have an effect on fetal growth rate and BW, our univariate analyses are given in Table 7.2.

Table 7.2. Multivariate analyses of surgery, maternal demographics and pregnancy characteristics with fetal growth rate and birthweight

Parameters	P value	
	Fetal growth rate	Birthweight
Surgery to conception interval	0.07	0.3
Total weight loss, %	**<0.01**	**<0.01**
Type of bariatric surgery		
Restrictive versus malabsorptive	0.27	0.18
Malabsorptive versus others	0.26	0.18
Gastric band versus others	0.19	0.19
Vertical sleeve gastrectomy versus others	0.96	0.74
Maternal age, yr	0.99	0.21
Maternal racial group (White versus others)	0.89	0.79
Maternal smoking, yes/no	0.39	0.21
Method of conception (spontaneous)	0.51	0.28
First trimester maternal body mass index, kg/m2	0.08	0.22
Development of preeclampsia, yes/no	0.47	0.87
Presence of glucose intolerance, yes/no	0.8	0.89
Gestational age at delivery, wk	-	**0.001**

The following correlations with fetal growth rate were found: surgery to conception interval (p=0.07), TWL (%) (p=<0.01) (Figure 7.1), type of bariatric surgery (p=0.27), maternal age (p=0.99), racial group (p=0.89), smoking (p=0.39), method of conception (p=0.51), first trimester maternal BMI (p=0.08), development of PE (p=0.47) and presence of glucose intolerance (p=0.80). First trimester maternal BMI, surgery to conception interval and TWL (%) were then entered into a multiple regression model and the latter remained a negatively correlated with fetal growth rate (p=0.04), even after adjustment for first trimester maternal BMI (p=0.76) and surgery to conception interval (p=0.26).

As far as BW is concerned, the following correlations were found: surgery to conception interval (p=0.30), TWL (%) (p=<0.01) (Figure 7.1), type of bariatric surgery (p=0.18), maternal age (p=0.21), racial group (p=0.79), smoking (p=0.21), method of conception

(p=0.28), first trimester maternal BMI (p=0.22), gestational age at delivery (p=0.001) development of PE (p=0.87) and presence of glucose intolerance (p=0.89). Maternal TWL and gestational age at delivery were then entered into a multiple regression model and TWL remained negatively correlated with BW (p=<0.01), even after adjustment for the gestational age at delivery (p<0.01). The results were unchanged if BMI reduction, instead of TWL, was examined.

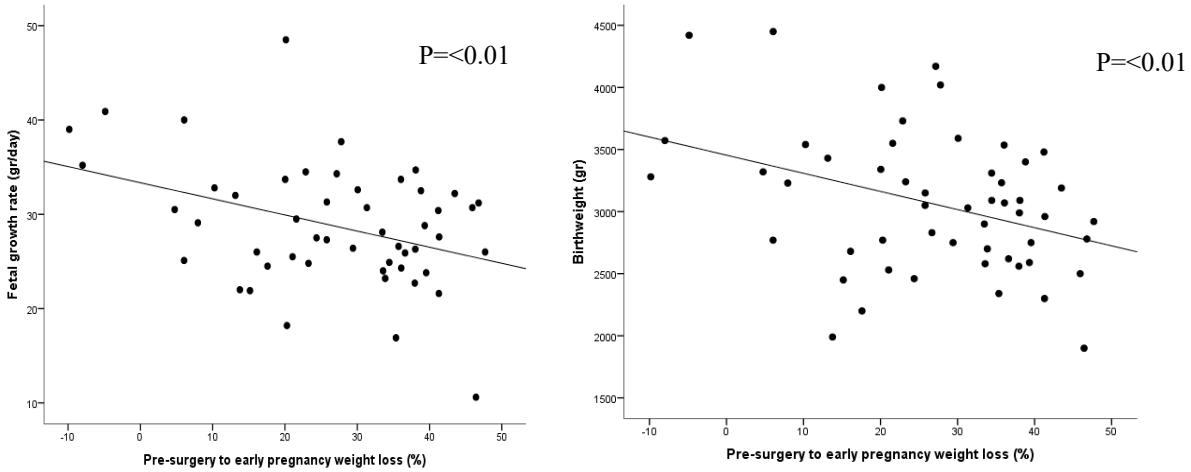


Figure 7.1 Correlation of maternal pre-surgery to early pregnancy weight loss and fetal growth rate (left) and birthweight (right)

Discussion

The study has showed that total maternal weight loss from pre-bariatric surgery to early pregnancy in nulliparous women has a negative association with fetal growth rate in the third trimester and BW. Conversely, surgery to conception time interval does not seem to have an impact on pregnancy and neonatal outcome in these women.

Weight loss following bariatric surgery is thought to be multifactorial and involving the BRAVE effect; **B**ile flow alteration, **R**eduction of gastric size, **A**natomical gut rearrangement and altered flow nutrients, **V**agal manipulation and **E**nteric gut hormone regulation. (261) Bariatric surgery and the decreased protein consumption has been shown to cause a breakdown of tissues and organs such as muscles. (262) Studies in pregnant mice have shown that maternal low protein diet changed the placental structure and function of the labyrinth zone and was associated with delayed spongiotrophoblast hyperplasia and hypertrophy. (263) Further animal studies have shown that protein restricted diet resulted in pre-pregnancy weight reduction, alteration in the placental vasculature with a reduction in total vascular length, surface area, volume and density together with a reduction in BW. (264) Studies in pregnant women have

also shown that inter-pregnancy weight reduction of ≥2 BMI units was associated with recurrent birth of an SGA neonate. (265) A population-based study looking at the effect of maternal weight change between pregnancies showed that obese women with inter-pregnancy BMI reduction of ≥ 8 BMI units had double the risk of delivering an SGA neonate. (266) Given these reported findings, we would anticipate that in higher weight loss, such as our population, (loss of 13 BMI units), the effect on BW would be more pronounced. In keeping with this, we have demonstrated that excessive maternal weight loss, following bariatric surgery, has an adverse impact on the in-utero growth and BW of the offspring. It is not possible to establish whether higher maternal weight loss is the result of surgically induced severe malabsorption or of the women's self-motivation. Regardless of method, weight loss is a measurable and modifiable factor. Our findings indicate that, the degree of weight loss, as a result of the surgery, could be adjusted, at least for women of reproductive age, in order to achieve the right balance between the anticipated benefits to the mother and the potential risk of adverse outcome in future pregnancies.

With regard to timing of conception, there is a general belief and recommendation that following bariatric surgery, pregnancy should be delayed for 12-24 months in order to avoid any adverse effects that rapid maternal weight loss can have on fetal development and weight. (251) However, studies have shown that surgery to conception interval, less or more than 12 or 18 months, does not have a negative effect on pregnancy outcomes. (252-254) Conversely, a recent study has shown that conception within 6 months of surgery may have a detrimental effect on BW. (267) Our study is in keeping with most of the previous findings showing that, surgery to conception interval was not an important predictor of fetal growth or BW, our population conceived on average 4 years following surgery.

A strength of our findings is that we prospectively studied, only, nulliparous women with previous bariatric surgery. Most of the studies assessing the effect of surgery on pregnancy outcomes have been retrospective and included both nulliparous and parous women. Parity, and especially delivery of a previous LGA neonate, is known to increase the BW and the risk of another large neonate in subsequent pregnancies, even after adjustment for other maternal characteristics. (258) Although all studies adjusted for parity, none of them considered the previous obstetric history in their analyses. Therefore, inclusion of parous women, the majority of who are likely to have had previous large babies in view of their high BMI, may have masked the effect of surgery-related characteristics to pregnancy outcome. In our study the pre-surgery

weight was self-reported and therefore there is a potential for re-call bias. However, women undergoing weight loss surgery are intrinsically aware of their weight, it is unlikely that this is a significant source of bias.

Conclusion

We have shown that in nulliparous women with previous bariatric surgery, excessive maternal weight loss, as a result of the surgery, appears to have a negative effect on fetal growth rate and BW of their offspring. Although larger future studies are needed to affirm our findings, consideration and guidance should be given to achieving an ideal weight loss, in women of reproductive age in order to prevent an adverse effect on the outcome of their future pregnancies.

Chapter 8

Final Summary and Discussion

Normal pregnancy requires significant cardiovascular changes and maladaptation along with cardiovascular reserve has been associated with developing hypertensive disorders and growth restriction. Obesity in pregnancy is associated with significant risks including hypertensive disorders, gestational diabetes and large-for-gestational-age neonates. With an increasingly obese population, bariatric surgery is a popular and effective treatment for sustained weight loss with the number of operations increasing yearly. Many of those undertaking bariatric surgery are women of childbearing age and pregnancy following bariatric surgery is known to reduce the risk of hypertensive disorders. Nevertheless, there are limited longitudinal studies on the cardiovascular adaptation to pregnancy in obese pregnant women and the cardiovascular adaptation in women with previous bariatric surgery has never previously been investigated. This thesis has sought to investigate the cardiovascular system in pregnancy in these groups of women to better understand the mechanisms behind the increased and decreased risk of hypertensive disorders in obese pregnant women and women following bariatric surgery respectively.

Principle findings

- Maternal cardiovascular adaptation in women with previous bariatric surgery compared to women with a similar pre-surgery BMI

Our study has found significant differences between the groups in maternal haemodynamic function, cardiac geometry and systolic and diastolic function. Maternal blood pressure, heart rate and cardiac output were lower and total peripheral resistance higher in the post-bariatric group. In the same group, maternal cardiac geometry differed with lower left ventricle mass and relative wall thickness, in addition diastolic and systolic indices were more favourable.

- Maternal cardiovascular adaptation in pregnancy in women with previous bariatric surgery compared to women with a similar early pregnancy BMI

The study found that pregnant women with previous bariatric surgery have better cardiovascular adaptation to pregnancy compared to women with similar early pregnancy BMI but no history of weight loss surgery. Haemodynamically, post-bariatric pregnant women demonstrated lower blood pressure, heart rate and cardiac output. Diastolic indices were more favourable in the post-bariatric women and systolic function, assessed by global longitudinal and global circumferential strain were both better in women with previous bariatric surgery. In contrast to the former study, we did not find any difference in cardiac geometry between the groups.

The findings from both of these studies suggest that bariatric surgery has a positive impact on the maternal cardiovascular adaptation, which appears to be beyond to what would be expected by weight loss as the latter study was closely matched for early pregnancy BMI. Cardiovascular changes in pregnant women after bariatric surgery could render these women less susceptible to the development of hypertension and therefore, give some theory to the lower prevalence of hypertensive disorders seen in this population. Our study could also inform national guidance regarding beneficial effects of bariatric surgery in obese women of reproductive age contemplating pregnancy.

- Maternal cardiovascular adaptation in pregnancy in obese pregnant women compared to women with a normal body mass index

This study has shown that, obese pregnant women have a different haemodynamic profile, altered cardiac geometry and impaired diastolic indices compared to pregnant women with a normal BMI. In particular, obese women have higher blood pressure, heart rate, stroke volume, cardiac output and lower total peripheral resistance. Furthermore, obese women demonstrated different geometry with higher left atrial diameter, left ventricle end diastolic diameter, posterior wall thickness, relative wall thickness, left ventricular mass and left ventricular mass index. In addition, there was evidence of impaired diastolic indices including lower mitral inflow E-wave/A-wave ratio and tissue Doppler imaging E' lateral/ E' medial and higher E/E' ratio compared to the normal BMI group. Our findings suggest suboptimal cardiac geometry, haemodynamic and diastolic function in the obese group. Obesity and hypertensive disorders in pregnancy both share similar cardiovascular features in their pre-clinical phase and cardiovascular maladaptation in obese pregnant women may play a role in the mechanism of hypertensive disorders in this population.

- Maternal cardiovascular indices and placental function in overweight/obese pregnant women

In our overweight/obese population we found that cardiac output and left atrial volume positively and total peripheral resistance negatively correlated with birthweight percentile. Furthermore, in the first trimester, left atrial volume negatively correlated with uterine artery pulsatility and systolic blood pressure in the second trimester negatively correlated with PAPP-A. These correlations remained significant even after adjustment for maternal characteristics. We build on existing evidence and show an association between maternal hemodynamic indices and placental function and birthweight in overweight/obese pregnant women.

- Effect of post-bariatric maternal weight loss and surgery to conception interval on perinatal outcomes of nulliparous women

This study showed that total maternal weight loss from pre-bariatric surgery to early pregnancy in nulliparous women has a negative association with fetal growth rate in the third trimester and BW. Conversely, surgery to conception time interval did not seem to have an impact on pregnancy and neonatal outcome in these women.

Limitations

Limitations of echocardiography

Although echocardiography is a non-invasive, inexpensive and easily accessible method for the cardiovascular assessment it has significant limitations. Technical issues include image quality and measurement errors. For the CO, measurement of LVOT diameter relies on the proper longitudinal plane and correct identification of the tissue-blood interface. As the CSA is proportional to the square of the diameter, any error made will also be squared. Accurate Doppler measurements relies on the ultrasound beam being parallel to the blood flow and a proper apical-5-chamber view is imperative. Doppler assessment of diastolic function requires parallel alignment of the Doppler beam and is heart rate and load dependant. The diagnosis of diastolic dysfunction involves a complex algorithm of several measurements. Estimation of EF also has significant drawbacks, it is dependant on image quality, foreshortening of the LV from transducer positioning errors is common, it requires geometric assumptions and is load dependant. Similarly, estimation of LV mass relies on geometric

assumptions and beam orientation, in addition, small errors are magnified by the formula. (268, 269)

Cardiac MRI represents the current gold standard in the non-invasive measurement of ventricular volumes, function and left ventricular mass. The technique is 3D and hence independent of geometrical assumptions, in addition there is clear definition of endocardial and epicardial borders making it highly accurate and reproducible. Furthermore, it has the ability to detect small changes in EF. However, for the purpose of this study cardiac MRI was not feasible due to accessibility and cost. (270) Superior to cardiac MRI is invasive cardiac catheterisation which has many diagnostic and therapeutic uses including coronary artery disease, measuring haemodynamics, evaluation of left ventricular function and the treatment of arrythmias and valve disease. The gold standard measurement for CO measurement is with pulmonary artery catheterisation. Cold saline is injected with the change in temperature measured downstream. In the Swan-Ganz method, catheters are fitted with a heated filament which heats the blood and measures the resultant thermodilution trace. Given that it is invasive, associated with significant risk and requires advanced skills and resources, it would not have been appropriate for this study.(271, 272)

Limitations of the study

There were several limitations to our study, unfortunately we did not have information on the pre-surgery or pre-pregnancy cardiac profile of the women with previous bariatric surgery and these factors, might have affected the cardiovascular function during pregnancy (Chapter 3 and 4). In spite of the women being closely matched for BMI, the weight loss incurred by the post-bariatric women is likely to have affected their cardiovascular function pre-pregnancy. Although the women with no-surgery were closely matched to the post-bariatric women, we had relatively small numbers and ideally would have included more women without surgery to achieve 1:2 or 1:3 matching. Due to the relatively small number of women in the post-bariatric group, we were unable to investigate the maternal cardiovascular function according to the type of surgery performed (gastric bypass, sleeve or band), or in cases of pregnancy induced hypertension or PE. In chapter 5 we compare normal BMI and obese pregnant women, unfortunately, due to time constraints, we had a small number (14) of women with normal BMI. Given the accessibility of low-risk pregnant women, this could have been expanded if resources had permitted.

Our results should be interpreted with caution as many parameters including the E/A ratio are load dependant and unadjusted for HR or volume. In order to minimise this, we also used TDI and strain via speckle tracking which are both less load dependant. Although we discuss reduced diastolic and systolic reserve or better function in one group over another, our results are still largely within the normal range and have not made a diagnosis of cardiac dysfunction in these women. The diagnosis of diastolic dysfunction involves a complex algorithm with several parameters, some of which we had not measured such as pulmonary venous flow. It is also pertinent to note the limitation in interpreting an association study due to the inability to prove causality. Further to this, although we have reported some significant associations, the R number is relatively low.

Challenges

Learning to perform and analyse the echocardiographs independently was challenging in itself but also compounded by difficult views due to breast enlargement in pregnancy and obesity. With limited statistical knowledge at the start of the project, I spent a significant amount of time learning how to perform the multilevel mixed model analysis. The longitudinal design gave power to our study but withdrawals and missing data led to challenges in our statistical analysis. In addition, matching post-bariatric women to no-surgery controls was challenged by the development of GDM at 28 weeks. Potentially a cohort design may have been simpler and increased sample size, however, the close matching of the groups gave strength to our findings.

Strengths

This thesis provides novel data on detailed maternal cardiovascular assessments of pregnancies with previous bariatric surgery. Although pregnant women with previous bariatric surgery are relatively rare, we managed to recruit enough women to provide significant results and with a longitudinal design adding strength to the findings. Several modalities within echocardiography were utilised including 2D imaging, TDI, M-mode and speckle tracking. In addition, following an intensive training period, all echocardiographic examinations were performed and analysed by experienced operators.

Future work

- Future work could include studies which separate the restrictive and malabsorptive procedures to further investigate the effects of surgery on the maternal cardiovascular system in pregnancy. In addition, strength to our findings could be achieved by including 1:2 or 1:3 matching of women with previous bariatric surgery and women without surgery.
- We could investigate women at term as most of late pre-eclampsia occurs at term it would be beneficial to understand the cardiovascular changes at this point to better understand the lower prevalence of hypertensive disorders in the post-bariatric surgery pregnant population. Similarly, our study of obese and normal BMI pregnant women could include a time point at term.
- The entero-cardiac axis could be investigated by measuring gut hormones such as leptin and GLP-1 and correlating them to cardiovascular parameters to further investigate the impact of bariatric surgery in the pregnant population.

References

1. World Health Organisation. Obesity and Overweight. Key facts. Feb 2018. [Available from: Obesity and overweight (who.int) (Accessed Jun 2021)
2. World Health Organisation. Prevalence of obesity age 18+ Female 2016 [Available from: global_obesity_2016_female.png (2027×1358) (who.int). (Accessed Jun 2021)
3. NHS Digital. Statistics on Obesity, Physical Activity and Diet. April 2018. [Available from: Statistics on Obesity, Physical Activity and Diet - NHS Digital (Accessed Jun 2020)
4. Eyre H, Kahn R, Robertson RM, null n, Clark NG, Doyle C, et al. Preventing Cancer, Cardiovascular Disease, and Diabetes. Circulation. 2004;109(25):3244-55.
5. Wang YC, McPherson K, Marsh T, Gortmaker SL, Brown M. Health and economic burden of the projected obesity trends in the USA and the UK. The Lancet. 2011;378(9793):815-25.
6. Vasan RS. Cardiac function and obesity. Heart. 2003;89(10):1127-9.
7. Wofford MR, Hall JE. Pathophysiology and treatment of obesity hypertension. Curr Pharm Des. 2004;10(29):3621-37.
8. Hall John E, do Carmo Jussara M, da Silva Alexandre A, Wang Z, Hall Michael E. Obesity-Induced Hypertension. Circulation Research. 2015;116(6):991-1006.
9. Seravalle G, Grassi G. Obesity and hypertension. Pharmacological Research. 2017;122:1-7.
10. Owen JG, Yazdi F, Reisin E. Bariatric Surgery and Hypertension. Am J Hypertens. 2017;31(1):11-7.

11. Oh YS. Arterial stiffness and hypertension. Clin Hypertens. 2018;24:17.
12. Jia G, Aroor AR, DeMarco VG, Martinez-Lemus LA, Meininger GA, Sowers JR. Vascular stiffness in insulin resistance and obesity. Front Physiol. 2015;6:231.
13. Alpert MA, Omran J, Bostick BP. Effects of Obesity on Cardiovascular Hemodynamics, Cardiac Morphology, and Ventricular Function. Curr Obes Rep. 2016;5(4):424-34.
14. Cuspidi C, Rescaldani M, Sala C, Grassi G. Left-ventricular hypertrophy and obesity: a systematic review and meta-analysis of echocardiographic studies. J Hypertens. 2014;32(1):16-25.
15. de Simone G, Devereux RB, Roman MJ, Alderman MH, Laragh JH. Relation of obesity and gender to left ventricular hypertrophy in normotensive and hypertensive adults. Hypertension. 1994;23(5):600-6.
16. Chahal H, McClelland RL, Tandri H, Jain A, Turkbey EB, Hundley WG, et al. Obesity and right ventricular structure and function: the MESA-Right Ventricle Study. Chest. 2012;141(2):388-95.
17. Alpert MA. Obesity cardiomyopathy: pathophysiology and evolution of the clinical syndrome. Am J Med Sci. 2001;321(4):225-36.
18. Cuspidi C, Rescaldani M, Tadic M, Sala C, Grassi G. Effects of bariatric surgery on cardiac structure and function: a systematic review and meta-analysis. Am J Hypertens. 2014;27(2):146-56.
19. Pascual M, Pascual DA, Soria F, Vicente T, Hernández AM, Tébar FJ, et al. Effects of isolated obesity on systolic and diastolic left ventricular function. Heart. 2003;89(10):1152-6.
20. Kaddoura S. Echo Made Easy. 3 ed: Elsevier; 2016. p.70-74.
21. Kaddoura S. Echo Made Easy. 3 ed: Elsevier. 2016. p. 133, 234-238.
22. Barbosa MM, Beleigoli AM, de Fatima Diniz M, Freire CV, Ribeiro AL, Nunes MC. Strain imaging in morbid obesity: insights into subclinical ventricular dysfunction. Clin Cardiol. 2011;34(5):288-93.
23. Tumuklu MM, Etikan I, Kisacik B, Kayikcioglu M. Effect of obesity on left ventricular structure and myocardial systolic function: assessment by tissue Doppler imaging and strain/strain rate imaging. Echocardiography. 2007;24(8):802-9.
24. Ruilope LM, Schmieder RE. Left ventricular hypertrophy and clinical outcomes in hypertensive patients. Am J Hypertens. 2008;21(5):500-8.
25. Willens HJ, Chakko SC, Lowery MH, Byers P, Labrador E, Gallagher A, et al. Tissue Doppler imaging of the right and left ventricle in severe obesity (body mass index >35 kg/m2). Am J Cardiol. 2004;94(8):1087-90.
26. Wong CY, O'Moore-Sullivan T, Leano R, Hukins C, Jenkins C, Marwick TH. Association of subclinical right ventricular dysfunction with obesity. J Am Coll Cardiol. 2006;47(3):611-6.
27. Foppa M, Arora G, Gona P, Ashrafi A, Salton CJ, Yeon SB, et al. Right Ventricular Volumes and Systolic Function by Cardiac Magnetic Resonance and the Impact of Sex, Age, and Obesity in a Longitudinally Followed Cohort Free of Pulmonary and Cardiovascular Disease: The Framingham Heart Study. Circ Cardiovasc Imaging. 2016;9(3):e003810.
28. May L. Cardiac Physiology of Pregnancy. Compr Physiol. 2015;5(3):1325-44.
29. Chandra S, Tripathi AK, Mishra S, Amzarul M, Vaish AK. Physiological changes in hematological parameters during pregnancy. Indian J Hematol Blood Transfus. 2012;28(3):144-6.
30. Sanghavi M, Rutherford JD. Cardiovascular physiology of pregnancy. Circulation. 2014;130(12):1003-8.

31. Hytten F. Blood volume changes in normal pregnancy. Clin Haematol. 1985;14(3):601-12.
32. Tan EK, Tan EL. Alterations in physiology and anatomy during pregnancy. Best Pract Res Clin Obstet Gynaecol. 2013;27(6):791-802.
33. Melchiorre K, Sharma R, Thilaganathan B. Cardiac structure and function in normal pregnancy. Curr Opin Obstet Gynecol. 2012;24(6):413-21.
34. Foo L, Tay J, Lees CC, McEniery CM, Wilkinson IB. Hypertension in pregnancy: natural history and treatment options. Curr Hypertens Rep. 2015;17(5):36.
35. Soma-Pillay P, Nelson-Piercy C, Tolppanen H, Mebazaa A. Physiological changes in pregnancy. Cardiovasc J Afr. 2016;27(2):89-94.
36. Hall ME, George EM, Granger JP. [The heart during pregnancy]. Rev Esp Cardiol. 2011;64(11):1045-50.
37. Melchiorre K, Sharma R, Khalil A, Thilaganathan B. Maternal Cardiovascular Function in Normal Pregnancy: Evidence of Maladaptation to Chronic Volume Overload. Hypertension. 2016;67(4):754-62.
38. Kametas NA, McAuliffe F, Cook B, Nicolaides KH, Chambers J. Maternal left ventricular transverse and long-axis systolic function during pregnancy. Ultrasound Obstet Gynecol. 2001;18(5):467-74.
39. Bamfo JE, Kametas NA, Nicolaides KH, Chambers JB. Maternal left ventricular diastolic and systolic long-axis function during normal pregnancy. Eur J Echocardiogr. 2007;8(5):360-8.
40. Zentner D, du Plessis M, Brennecke S, Wong J, Grigg L, Harrap SB. Deterioration in cardiac systolic and diastolic function late in normal human pregnancy. Clin Sci (Lond). 2009;116(7):599-606.
41. Kaddoura S. Echo Made Easy. 3 ed: Elsevier; 2016. p. 113-117.
42. Visentin S, Palermo C, Camerin M, Daliento L, Muraru D, Cosmi E, et al. Echocardiographic Techniques of Deformation Imaging in the Evaluation of Maternal Cardiovascular System in Patients with Complicated Pregnancies. Biomed Res Int. 2017;2017:4139635.
43. Cong J, Fan T, Yang X, Squires JW, Cheng G, Zhang L, et al. Structural and functional changes in maternal left ventricle during pregnancy: a three-dimensional speckle-tracking echocardiography study. Cardiovasc Ultrasound. 2015;13:6.
44. Moran AM, Colan SD, Mauer MB, Geva T. Adaptive mechanisms of left ventricular diastolic function to the physiologic load of pregnancy. Clin Cardiol. 2002;25(3):124-31.
45. Melchiorre K, Thilaganathan B. Maternal cardiac function in preeclampsia. Curr Opin Obstet Gynecol. 2011;23(6):440-7.
46. Foo FL, Mahendru AA, Masini G, Fraser A, Cacciatore S, MacIntyre DA, et al. Association Between Prepregnancy Cardiovascular Function and Subsequent Preeclampsia or Fetal Growth Restriction. Hypertension. 2018;72(2):442-50.
47. Thilaganathan B, Kalafat E. Cardiovascular System in Preeclampsia and Beyond. Hypertension. 2019;73(3):522-31.
48. Ananth CV, Keyes KM, Wapner RJ. Pre-eclampsia rates in the United States, 1980-2010: age-period-cohort analysis. BMJ (Clinical research ed). 2013;347:f6564-f.
49. Hendy E, Vousden N, Shennan A, Chappell L. OP 35 Incidence of pre-eclampsia in the UK in 2016–17. Pregnancy Hypertension: An International Journal of Women's Cardiovascular Health. 2017;9:25.
50. Ditisheim A, Wuerzner G, Ponte B, Vial Y, Irion O, Burnier M, et al. Prevalence of Hypertensive Phenotypes After Preeclampsia. Hypertension. 2018;71(1):103-9.

51. Behrens I, Basit S, Melbye M, Lykke JA, Wohlfahrt J, Bundgaard H, et al. Risk of post-pregnancy hypertension in women with a history of hypertensive disorders of pregnancy: nationwide cohort study. BMJ. 2017;358:j3078.
52. Savu O, Jurcuţ R, Giuşcă S, van Mieghem T, Gussi I, Popescu BA, et al. Morphological and functional adaptation of the maternal heart during pregnancy. Circ Cardiovasc Imaging. 2012;5(3):289-97.
53. 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(4):496-504.
54. Castleman JS, Ganapathy R, Taki F, Lip GY, Steeds RP, Kotecha D. Echocardiographic Structure and Function in Hypertensive Disorders of Pregnancy: A Systematic Review. Circ Cardiovasc Imaging. 2016;9(9).
55. Valensise H, Vasapollo B, Gagliardi G, Novelli GP. Early and late preeclampsia: two different maternal hemodynamic states in the latent phase of the disease. Hypertension. 2008;52(5):873-80.
56. Tay J, Foo L, Masini G, Bennett PR, McEniery CM, Wilkinson IB, et al. 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(5):517.e1-.e12.
57. Staff AC, Redman CWG. The Differences Between Early- and Late-Onset Pre-eclampsia. In: Saito S, editor. Preeclampsia: Basic, Genomic, and Clinical. Singapore: Springer Singapore; 2018. p. 157-72.
58. Guy GP, Ling HZ, Machuca M, Poon LC, Nicolaides KH. Maternal cardiac function at 35-37 weeks' gestation: relationship with birth weight. Ultrasound Obstet Gynecol. 2017;49(1):67-72.
59. Mahendru AA, Foo FL, McEniery CM, Everett TR, Wilkinson IB, Lees CC. Change in maternal cardiac output from preconception to mid-pregnancy is associated with birth weight in healthy pregnancies. Ultrasound Obstet Gynecol. 2017;49(1):78-84.
60. Denison FC, Aedla NR, Keag O, Hor K, Reynolds RM, Milne A, et al. Care of Women with Obesity in Pregnancy: Green-top Guideline No. 72. BJOG. 2018.
61. Weiss JL, Malone FD, Emig D, Ball RH, Nyberg DA, Comstock CH, et al. Obesity, obstetric complications and cesarean delivery rate--a population-based screening study. Am J Obstet Gynecol. 2004;190(4):1091-7.
62. Duckitt K, Harrington D. Risk factors for pre-eclampsia at antenatal booking: systematic review of controlled studies. BMJ. 2005;330(7491):565.
63. O'Brien TE, Ray JG, Chan WS. Maternal body mass index and the risk of preeclampsia: a systematic overview. Epidemiology. 2003;14(3):368-74.
64. Mbah AK, Kornosky JL, Kristensen S, August EM, Alio AP, Marty PJ, et al. Super-obesity and risk for early and late pre-eclampsia. BJOG. 2010;117(8):997-1004.
65. Jeyabalan A. Epidemiology of preeclampsia: impact of obesity. Nutr Rev. 2013;71 Suppl 1:S18-25.
66. Yu CK, Teoh TG, Robinson S. Obesity in pregnancy. BJOG. 2006;113(10):1117-25.
67. Health. NDoP, MBRRACE-UK: Saving Lives IMC. Lessons learned to inform maternity care from the UK and Ireland Confidential Enquiries into Maternal Deaths and Morbidity 2014–16. 2018.
68. Fitzsimons KJ, Modder J, Greer IA. Obesity in pregnancy: risks and management. Obstet Med. 2009;2(2):52-62.
69. Norman JE, Reynolds RM, Reynolds R. The consequences of obesity and excess weight gain in pregnancy. Proc Nutr Soc. 2011;70(4):450-6.

70. Dennis AT, Castro JM, Ong M, Carr C. Haemodynamics in obese pregnant women. Int J Obstet Anesth. 2012;21(2):129-34.
71. Veille JC, Hanson R. Obesity, pregnancy, and left ventricular functioning during the third trimester. Am J Obstet Gynecol. 1994;171(4):980-3.
72. Buddeberg BS, Sharma R, O'Driscoll JM, Kaelin Agten A, Khalil A, Thilaganathan B. Cardiac maladaptation in obese pregnancy at term. Ultrasound Obstet Gynecol. 2018.
73. Vinayagam D, Gutierrez J, Binder J, Mantovani E, Thilaganathan B, Khalil A. Impaired maternal hemodynamics in morbidly obese women: a case-control study. Ultrasound Obstet Gynecol. 2017;50(6):761-5.
74. Vonck S, Lanssens D, Staelens AS, Tomsin K, Oben J, Bruckers L, et al. Obesity in pregnancy causes a volume overload in third trimester. Eur J Clin Invest. 2019;49(11):e13173.
75. Wilson PF, D'Agostino RB, Sullivan L, Parise H, Kannel WB. Overweight and obesity as determinants of cardiovascular risk: The framingham experience. Archives of Internal Medicine. 2002;162(16):1867-72.
76. Tuah NA, Amiel C, Qureshi S, Car J, Kaur B, Majeed A. Transtheoretical model for dietary and physical exercise modification in weight loss management for overweight and obese adults. Cochrane Database Syst Rev. 2011(10):CD008066.
77. Mingrone G, Panunzi S, De Gaetano A, Guidone C, Iaconelli A, Leccesi L, et al. Bariatric surgery versus conventional medical therapy for type 2 diabetes. N Engl J Med. 2012;366(17):1577-85.
78. Colquitt J, Clegg A, Loveman E, Royle P, Sidhu MK. Surgery for morbid obesity. Cochrane Database Syst Rev. 2005(4):CD003641.
79. Buchwald H, Estok R, Fahrbach K, Banel D, Jensen MD, Pories WJ, et al. Weight and type 2 diabetes after bariatric surgery: systematic review and meta-analysis. Am J Med. 2009;122(3):248-56.e5.
80. Adams TD, Gress RE, Smith SC, Halverson RC, Simper SC, Rosamond WD, et al. Long-term mortality after gastric bypass surgery. N Engl J Med. 2007;357(8):753-61.
81. National Institure for Health and Care Excellence. Obesity: identification, assessment and management 2014 [Available from: https://www.nice.org.uk/guidance/cg189/chapter/1-Recommendations.(Accessed: May 2020)
82. National Institute of Health Research Southampton Biomedical Research Centre. Surgical treatment of obesity : University Hospital Southampton NHS Trust; 2013 [Available from: http://www.uhs.nhs.uk/ClinicalResearchinSouthampton/Research/Facilities/NIHR-Southampton-Biomedical-Research-Centre/Ourresearchandimpacts/Impactcasestudies/Southamptonresearchpartofnationaldrivetotackleobesity.aspx (Accessed: Sept 2020)
83. Buchwald H, Avidor Y, Braunwald E, Jensen MD, Pories W, Fahrbach K, et al. Bariatric surgery: a systematic review and meta-analysis. JAMA. 2004;292(14):1724-37.
84. National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). Bariatric Surgery. 2018. [Available from: https://www.niddk.nih.gov/health-information/weight-management/bariatric-surgery (Accessed Sept 2020)
85. Surgery ASfMaB. Bariatric Surgery Procedures.
86. Sjöström CD, Lissner L, Wedel H, Sjöström L. Reduction in incidence of diabetes, hypertension and lipid disturbances after intentional weight loss induced by bariatric surgery: the SOS Intervention Study. Obes Res. 1999;7(5):477-84.
87. Wilhelm SM, Young J, Kale-Pradhan PB. Effect of bariatric surgery on hypertension: a meta-analysis. Ann Pharmacother. 2014;48(6):674-82.

88. van Brussel PM, van den Bogaard B, de Weijer BA, Truijen J, Krediet CT, Janssen IM, et al. Blood pressure reduction after gastric bypass surgery is explained by a decrease in cardiac output. J Appl Physiol (1985). 2017;122(2):223-9.
89. Pedersen JS, Borup C, Damgaard M, Yatawara VD, Floyd AK, Gadsbøll N, et al. Early 24-hour blood pressure response to Roux-en-Y gastric bypass in obese patients. Scand J Clin Lab Invest. 2017;77(1):53-9.
90. Ahmed AR, Rickards G, Coniglio D, Xia Y, Johnson J, Boss T, et al. Laparoscopic Roux-en-Y Gastric Bypass and Its Early Effect on Blood Pressure. Obesity Surgery. 2009;19(7):845-9.
91. Aggarwal R, Harling L, Efthimiou E, Darzi A, Athanasiou T, Ashrafian H. The Effects of Bariatric Surgery on Cardiac Structure and Function: a Systematic Review of Cardiac Imaging Outcomes. Obes Surg. 2016;26(5):1030-40.
92. Ashrafian H, le Roux CW, Darzi A, Athanasiou T. Effects of bariatric surgery on cardiovascular function. Circulation. 2008;118(20):2091-102.
93. Ashrafian H, Athanasiou T, le Roux CW. Heart remodelling and obesity: the complexities and variation of cardiac geometry. Heart. 2011;97(3):171-2.
94. Laferrère B, Teixeira J, McGinty J, Tran H, Egger JR, Colarusso A, et al. Effect of weight loss by gastric bypass surgery versus hypocaloric diet on glucose and incretin levels in patients with type 2 diabetes. J Clin Endocrinol Metab. 2008;93(7):2479-85.
95. le Roux CW, Welbourn R, Werling M, Osborne A, Kokkinos A, Laurenius A, et al. Gut Hormones as Mediators of Appetite and Weight Loss After Roux-en-Y Gastric Bypass. Annals of Surgery. 2007;246(5).
96. Wickremesekera K, Miller G, Naotunne TD, Knowles G, Stubbs RS. Loss of Insulin Resistance after Roux-en-Y Gastric Bypass Surgery: a Time Course Study. Obesity Surgery. 2005;15(4):474-81.
97. Gutzwiller J-P, Tschopp S, Bock A, Zehnder CE, Huber AR, Kreyenbuehl M, et al. Glucagon-Like Peptide 1 Induces Natriuresis in Healthy Subjects and in Insulin-Resistant Obese Men. The Journal of Clinical Endocrinology & Metabolism. 2004;89(6):3055-61.
98. Jeppe S, Jens Juul H, Jens Peter G, Jørgen F, Jens Sandahl C. Glucagon-like peptide-1: effect on pro-atrial natriuretic peptide in healthy males. Endocrine Connections. 2014;3(1):11-6.
99. Bravo PE, Morse S, Borne DM, Aguilar EA, Reisin E. Leptin and hypertension in obesity. Vasc Health Risk Manag. 2006;2(2):163-9.
100. Beckman LM, Beckman TR, Earthman CP. Changes in Gastrointestinal Hormones and Leptin after Roux-en-Y Gastric Bypass Procedure: A Review. Journal of the American Dietetic Association. 2010;110(4):571-84.
101. Korner J, Bessler M, Cirilo LJ, Conwell IM, Daud A, Restuccia NL, et al. Effects of Roux-en-Y Gastric Bypass Surgery on Fasting and Postprandial Concentrations of Plasma Ghrelin, Peptide YY, and Insulin. The Journal of Clinical Endocrinology & Metabolism. 2005;90(1):359-65.
102. Owan T, Avelar E, Morley K, Jiji R, Hall N, Krezowski J, et al. Favorable changes in cardiac geometry and function following gastric bypass surgery: 2-year follow-up in the Utah obesity study. J Am Coll Cardiol. 2011;57(6):732-9.
103. Garza CA, Pellikka PA, Somers VK, Sarr MG, Collazo-Clavell ML, Korenfeld Y, et al. Structural and functional changes in left and right ventricles after major weight loss following bariatric surgery for morbid obesity. Am J Cardiol. 2010;105(4):550-6.
104. Graziani F, Leone AM, Cialdella P, Basile E, Pennestrì F, Della Bona R, et al. Effects of bariatric surgery on cardiac remodeling: clinical and pathophysiologic implications. Int J Cardiol. 2013;168(4):4277-9.

105. Grapsa J, Tan TC, Paschou SA, Kalogeropoulos AS, Shimony A, Kaier T, et al. The effect of bariatric surgery on echocardiographic indices: a review of the literature. Eur J Clin Invest. 2013;43(11):1224-30.
106. Kardassis D, Bech-Hanssen O, Schönander M, Sjöström L, Petzold M, Karason K. Impact of body composition, fat distribution and sustained weight loss on cardiac function in obesity. Int J Cardiol. 2012;159(2):128-33.
107. Homsy. E, Bradley. D, Bradley. E. Does the Right Heart Benefit From Bariatric Surgery? Chest2016. p. 1185A.
108. Kaier TE, Morgan D, Grapsa J, Demir OM, Paschou SA, Sundar S, et al. Ventricular remodelling post-bariatric surgery: is the type of surgery relevant? A prospective study with 3D speckle tracking. Eur Heart J Cardiovasc Imaging. 2014;15(11):1256-62.
109. Shin SH, Lee YJ, Heo YS, Park SD, Kwon SW, Woo SI, et al. Beneficial Effects of Bariatric Surgery on Cardiac Structure and Function in Obesity. Obes Surg. 2017;27(3):620-5.
110. Mostfa SA. Impact of obesity and surgical weight reduction on cardiac remodeling. Indian Heart Journal2018.
111. Galazis N, Docheva N, Simillis C, Nicolaides KH. Maternal and neonatal outcomes in women undergoing bariatric surgery: a systematic review and meta-analysis. Eur J Obstet Gynecol Reprod Biol. 2014;181:45-53.
112. Schauer PR, Kashyap SR, Wolski K, Brethauer SA, Kirwan JP, Pothier CE, et al. Bariatric Surgery versus Intensive Medical Therapy in Obese Patients with Diabetes. New England Journal of Medicine. 2012;366(17):1567-76.
113. Dixon JB, Dixon ME, O'Brien PE. Birth outcomes in obese women after laparoscopic adjustable gastric banding. Obstet Gynecol. 2005;106(5 Pt 1):965-72.
114. Johansson K, Cnattingius S, Näslund I, Roos N, Trolle Lagerros Y, Granath F, et al. Outcomes of pregnancy after bariatric surgery. N Engl J Med. 2015;372(9):814-24.
115. Sheiner E, Levy A, Silverberg D, Menes TS, Levy I, Katz M, et al. Pregnancy after bariatric surgery is not associated with adverse perinatal outcome. Am J Obstet Gynecol. 2004;190(5):1335-40.
116. Vrebosch L, Bel S, Vansant G, Guelinckx I, Devlieger R. Maternal and neonatal outcome after laparoscopic adjustable gastric banding: a systematic review. Obes Surg. 2012;22(10):1568-79.
117. Berlac JF, Skovlund CW, Lidegaard O. Obstetrical and neonatal outcomes in women following gastric bypass: a Danish national cohort study. Acta Obstet Gynecol Scand. 2014;93(5):447-53.
118. Ducarme G, Revaux A, Rodrigues A, Aissaoui F, Pharisien I, Uzan M. Obstetric outcome following laparoscopic adjustable gastric banding. Int J Gynaecol Obstet. 2007;98(3):244-7.
119. Maggard MA, Yermilov I, Li Z, Maglione M, Newberry S, Suttorp M, et al. Pregnancy and fertility following bariatric surgery: a systematic review. Jama. 2008;300(19):2286-96.
120. British and Irish Hypertension Society. How to measure Blood Pressure [Available from: https://bihsoc.org/resources/bp-measurement/measure-blood-pressure/. (Accessed May 2018)
121. Robinson HP, Fleming JE. A critical evaluation of sonar "crown-rump length" measurements. Br J Obstet Gynaecol. 1975;82(9):702-10.
122. Santorum M, Wright D, Syngelaki A, Karagioti N, Nicolaides KH. Accuracy of first-trimester combined test in screening for trisomies 21, 18 and 13. Ultrasound Obstet Gynecol. 2017;49(6):714-20.

123. Salomon LJ, Alfirevic Z, Berghella V, Bilardo C, Hernandez-Andrade E, Johnsen SL, et al. Practice guidelines for performance of the routine mid-trimester fetal ultrasound scan. Ultrasound Obstet Gynecol. 2011;37(1):116-26.
124. Mari G, Deter RL. Middle cerebral artery flow velocity waveforms in normal and small-for-gestational-age fetuses. American Journal of Obstetrics and Gynecology. 1992;166(4):1262-70.
125. Akolekar R, Syngelaki A, Gallo DM, Poon LC, Nicolaides KH. Umbilical and fetal middle cerebral artery Doppler at 35-37 weeks' gestation in the prediction of adverse perinatal outcome. Ultrasound Obstet Gynecol. 2015;46(1):82-92.
126. Nicolaides N RG, Hecher K. Doppler studies in fetal hypoxemic hypoxia: Fetal Medicine Foundation; 2002 [Available from: https://fetalmedicine.org/var/uploads/web/Doppler/Doppler%20Ultrasound%20-%20Hypoxia%20in%20FGR.pdf. (Accessed June 2021)
127. Adam S, Ammori B, Soran H, Syed AA. Pregnancy after bariatric surgery: screening for gestational diabetes. BMJ. 2017;356:j533.
128. National Institute for Helath and Care Excellence. Diabetes in pregnancy: management from preconception to the postnatal period: National Institute for Health and Clinical Excellence; 2015 [Available from: Recommendations | Diabetes in pregnancy: management from preconception to the postnatal period | Guidance | NICE (Accessed June 2019)
130. Burton GJ, Redman CW, Roberts JM, Moffett A. Pre-eclampsia: pathophysiology and clinical implications. BMJ. 2019;366:l2381.
131. Nicolaides KH, Wright D, Syngelaki A, Wright A, Akolekar R. Fetal Medicine Foundation fetal and neonatal population weight charts. Ultrasound in Obstetrics & Gynecology. 2018;52(1):44-51.
132. Otto CM. Textbook of Clinical Echocardiography E-Book: Elsevier Health Sciences; 2016.
133. Mohamed AA, Arifi AA, Omran A. The basics of echocardiography. Journal of the Saudi Heart Association. 2010;22(2):71-6.
134. Kaddoura S. Echo Made Easy 1-13. 3 ed: Elsevier; 2016.
135. Mitchell C, Rahko PS, Blauwet LA, Canaday B, Finstuen JA, Foster MC, et al. Guidelines for Performing a Comprehensive Transthoracic Echocardiographic Examination in Adults: Recommendations from the American Society of Echocardiography. J Am Soc Echocardiogr. 2019;32(1):1-64.
136. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for Cardiac Chamber Quantification by Echocardiography in Adults: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Journal of the American Society of Echocardiography. 2015;28(1):1-39.e14.
137. Kaddoura S. Echo Made Easy. 3 ed: Elsevier; 2016. p. 93-103.
138. British Society of Echocardiography. Echocardiography: Guidelines for Chamber Quantification [Available from: https://www.bsecho.org/media/40506/chamber-final-2011_2_.pdf. (Accessed May 2018)
139. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, et al. Recommendations for chamber quantification *. European Journal of Echocardiography. 2006;7(2):79-108.
140. Hu K, Liu D, Herrmann S, Niemann M, Gaudron PD, Voelker W, et al. Clinical implication of mitral annular plane systolic excursion for patients with cardiovascular disease. European Heart Journal - Cardiovascular Imaging. 2013;14(3):205-12.
141. Kaddoura S. Echo Made Easy. 3 ed: Elsevier; 2016. p. 59-62.

142. Wang Y, Moss J, Thisted R. Predictors of body surface area. J Clin Anesth. 1992;4(1):4-10.
143. Szauder I, Kovács A, Pavlik G. Comparison of left ventricular mechanics in runners versus bodybuilders using speckle tracking echocardiography. Cardiovasc Ultrasound. 2015;13:7.
144. Blessberger H, Binder T. Two dimensional speckle tracking echocardiography: basic principles. Heart. 2010;96(9):716.
145. Koo TK, Li MY. A Guideline of Selecting and Reporting Intraclass Correlation Coefficients for Reliability Research. Journal of Chiropractic Medicine. 2016;15(2):155-63.
146. Kleijn SA, Aly MFA, Terwee CB, van Rossum AC, Kamp O. Reliability of left ventricular volumes and function measurements using three-dimensional speckle tracking echocardiography. European Heart Journal - Cardiovascular Imaging. 2012;13(2):159-68.
147. Goldstein H, Browne W, Rasbash J. Multilevel modelling of medical data. Statistics in Medicine. 2002;21(21):3291-315.
148. Ling HZ, Guy GP, Bisquera A, Poon LC, Nicolaides KH, Kametas NA. The effect of parity on longitudinal maternal hemodynamics. American Journal of Obstetrics and Gynecology. 2019;221(3):249.e1-.e14.
149. Sjöström L. Review of the key results from the Swedish Obese Subjects (SOS) trial - a prospective controlled intervention study of bariatric surgery. J Intern Med. 2013;273(3):219-34.
150. Piche M, Clavel MA, Pibarot P, Poirier P. P924 Benefits of bariatric surgery on subclinical myocardial function using global longitudinal strain in severely obese individuals with and without diabetes. European Heart Journal - Cardiovascular Imaging. 2020;21(Supplement_1).
151. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2015;28(1):1-39.e14.
152. Faul F, Erdfelder E, Lang AG, Buchner A. G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav Res Methods. 2007;39(2):175-91.
153. Bueter M, Ahmed A, Ashrafian H, le Roux CW. Bariatric surgery and hypertension. Surgery for Obesity and Related Diseases. 2009;5(5):615-20.
154. Connell JMC, Davies E. The new biology of aldosterone. Journal of Endocrinology. 2005;186(1):1-20.
155. Abodeely A, Roye GD, Harrington DT, Cioffi WG. Pregnancy outcomes after bariatric surgery: maternal, fetal, and infant implications. Surgery for Obesity and Related Diseases. 2008;4(3):464-71.
156. O'Brien PD, Hinder LM, Callaghan BC, Feldman EL. Neurological consequences of obesity. The Lancet Neurology. 2017;16(6):465-77.
157. Pouwels S, Lascaris B, Nienhuijs SW, Bouwman AR, Buise MP. Short-Term Changes in Cardiovascular Hemodynamics in Response to Bariatric Surgery and Weight Loss Using the Nexfin® Non-invasive Continuous Monitoring Device: a Pilot Study. Obes Surg. 2017;27(7):1835-41.
158. Nault I, Nadreau E, Paquet C, Brassard P, Marceau P, Marceau S, et al. Impact of bariatric surgery–induced weight loss on heart rate variability. Metabolism. 2007;56(10):1425-30.
159. Wasmund SL, Owan T, Yanowitz FG, Adams TD, Hunt SC, Hamdan MH, et al. Improved heart rate recovery after marked weight loss induced by gastric bypass surgery: Two-year follow up in the Utah Obesity Study. Heart Rhythm. 2011;8(1):84-90.

160. Lambert EA, Rice T, Eikelis N, Straznicky NE, Lambert GW, Head GA, et al. Sympathetic Activity and Markers of Cardiovascular Risk in Nondiabetic Severely Obese Patients: The Effect of the Initial 10% Weight Loss. American Journal of Hypertension. 2014;27(10):1308-15.
161. Lascaris B, Pouwels S, Houthuizen P, Dekker LR, Nienhuijs SW, Bouwman RA, et al. Cardiac structure and function before and after bariatric surgery: a clinical overview. Clinical Obesity. 2018;8(6):434-43.
162. Hennessy TG, MacDonald D, Hennessy MS, Maguire M, Blake S, McCann HA, et al. Serial changes in cardiac output during normal pregnancy: a Doppler ultrasound study. European Journal of Obstetrics & Gynecology and Reproductive Biology. 1996;70(2):117-22.
163. Desai DK, Moodley J, Naidoo DP. Echocardiographic Assessment of Cardiovascular Hemodynamics in Normal Pregnancy. Obstetrics & Gynecology. 2004;104(1).
164. Meah VL, Cockcroft JR, Backx K, Shave R, Stöhr EJ. Cardiac output and related haemodynamics during pregnancy: a series of meta-analyses. Heart. 2016;102(7):518-26.
165. Thornburg KL, Jacobson S-L, Giraud GD, Morton MJ. Hemodynamic changes in pregnancy. Seminars in Perinatology. 2000;24(1):11-4.
166. Kametas NA, McAuliffe F, Hancock J, Chambers J, Nicolaides KH. Maternal left ventricular mass and diastolic function during pregnancy. Ultrasound in Obstetrics & Gynecology. 2001;18(5):460-6.
167. Vest AR, Heneghan HM, Agarwal S, Schauer PR, Young JB. Bariatric surgery and cardiovascular outcomes: a systematic review. Heart. 2012;98(24):1763-77.
168. Jong CJ, Yeung J, Tseung E, Karmazyn M. Leptin-induced cardiomyocyte hypertrophy is associated with enhanced mitochondrial fission. Mol Cell Biochem. 2019;454(1-2):33-44.
169. Estensen ME, Beitnes JO, Grindheim G, Aaberge L, Smiseth OA, Henriksen T, et al. Altered maternal left ventricular contractility and function during normal pregnancy. Ultrasound in Obstetrics & Gynecology. 2013;41(6):659-66.
170. Patel J, Rikhi R, Hussain M, Ayoub C, Klein A, Collier P, et al. Global longitudinal strain is a better metric than left ventricular ejection fraction: lessons learned from cancer therapeutic-related cardiac dysfunction. Curr Opin Cardiol. 2020;35(2):170-7.
171. Frea S, Andreis A, Scarlatta V, Rovera C, Vairo A, Pistone E, et al. Subclinical Left Ventricular Dysfunction in Severe Obesity and Reverse Cardiac Remodeling after Bariatric Surgery. J Cardiovasc Echogr. 2020;30(1):22-8.
172. Sheiner E, Willis K, Yogev Y. Bariatric Surgery: Impact on Pregnancy Outcomes. Current Diabetes Reports. 2013;13(1):19-26.
173. De Paco C, Kametas N, Rencoret G, Strobl I, Nicolaides KH. Maternal Cardiac Output Between 11 and 13 Weeks of Gestation in the Prediction of Preeclampsia and Small for Gestational Age. Obstetrics & Gynecology. 2008;111(2).
174. Samson R, Ayinapudi K, Le Jemtel TH, Oparil S. Obesity, Hypertension, and Bariatric Surgery. Current Hypertension Reports. 2020;22(7):46.
175. Curry TB, Somaraju M, Hines CN, Groenewald CB, Miles JM, Joyner MJ, et al. Sympathetic support of energy expenditure and sympathetic nervous system activity after gastric bypass surgery. Obesity. 2013;21(3):480-5.
176. Grassi G, Seravalle G, Cattaneo BM, Bolla GB, Lanfranchi A, Colombo M, et al. Sympathetic activation in obese normotensive subjects. Hypertension. 1995;25(4 Pt 1):560-3.
177. Rahmouni K, Morgan DA, Morgan GM, Liu X, Sigmund CD, Mark AL, et al. Hypothalamic PI3K and MAPK differentially mediate regional sympathetic activation to insulin. The Journal of clinical investigation. 2004;114(5):652-8.

178. Hall JE, Hildebrandt DA, Kuo J. Obesity hypertension: role of leptin and sympathetic nervous system*. American Journal of Hypertension. 2001;14(S3):103S-15S.
179. Rahmouni K, Correia Marcelo LG, Haynes William G, Mark Allyn L. Obesity-Associated Hypertension. Hypertension. 2005;45(1):9-14.
180. Kazumi T, Kawaguchi A, Katoh J, Iwahashi M, Yoshino G. Fasting insulin and leptin serum levels are associated with systolic blood pressure independent of percentage body fat and body mass index. J Hypertens. 1999;17(10):1451-5.
181. Manning S, Pucci A, Batterham RL. GLP-1: A Mediator of the Beneficial Metabolic Effects of Bariatric Surgery? Physiology. 2015;30(1):50-62.
182. Hallersund P, Sjöström L, Olbers T, Lönroth H, Jacobson P, Wallenius V, et al. Gastric Bypass Surgery Is Followed by Lowered Blood Pressure and Increased Diuresis - Long Term Results from the Swedish Obese Subjects (SOS) Study. PLOS ONE. 2012;7(11):e49696.
183. Seravalle G, Colombo M, Perego P, Giardini V, Volpe M, Dell'Oro R, et al. Long-Term Sympathoinhibitory Effects of Surgically Induced Weight Loss in Severe Obese Patients. Hypertension. 2014;64(2):431-7.
184. KjÆR MM, Nilas L. Pregnancy after bariatric surgery – a review of benefits and risks. Acta Obstetricia et Gynecologica Scandinavica. 2013;92(3):264-71.
185. de Simone G, Devereux Richard B, Daniels Stephen R, Mureddu G, Roman Mary J, Kimball Thomas R, et al. Stroke Volume and Cardiac Output in Normotensive Children and Adults. Circulation. 1997;95(7):1837-43.
186. Stelfox HT, Ahmed SB, Ribeiro RA, Gettings EM, Pomerantsev E, Schmidt U. Hemodynamic monitoring in obese patients: The impact of body mass index on cardiac output and stroke volume*. Critical Care Medicine. 2006;34(4).
187. Jhaveri RR, Pond KK, Hauser TH, Kissinger KV, Goepfert L, Schneider B, et al. Cardiac remodeling after substantial weight loss: a prospective cardiac magnetic resonance study after bariatric surgery. Surgery for Obesity and Related Diseases. 2009;5(6):648-52.
188. Perego L, Pizzocri P, Corradi D, Maisano F, Paganelli M, Fiorina P, et al. Circulating Leptin Correlates with Left Ventricular Mass in Morbid (Grade III) Obesity before and after Weight Loss Induced by Bariatric Surgery: A Potential Role for Leptin in Mediating Human Left Ventricular Hypertrophy. The Journal of Clinical Endocrinology & Metabolism. 2005;90(7):4087-93.
189. Algahim MF, Lux TR, Leichman JG, Boyer AF, Miller CC, Laing ST, et al. Progressive Regression of Left Ventricular Hypertrophy Two Years after Bariatric Surgery. The American Journal of Medicine. 2010;123(6):549-55.
190. Mesa A, Jessurun C, Hernandez A, Adam K, Brown D, Vaughn William K, et al. Left Ventricular Diastolic Function in Normal Human Pregnancy. Circulation. 1999;99(4):511-7.
191. Nguyen TD, Shingu Y, Amorim PA, Schenkl C, Schwarzer M, Doenst T. GLP-1 Improves Diastolic Function and Survival in Heart Failure with Preserved Ejection Fraction. Journal of Cardiovascular Translational Research. 2018;11(3):259-67.
192. Nathanson D, Zethelius B, Berne C, Lind L, Andrén B, Ingelsson E, et al. Plasma levels of glucagon like peptide-1 associate with diastolic function in elderly men. Diabet Med. 2011;28(3):301-5.
193. Wang XH, Han LN, Yu YR, Wang C, Wang B, Wen XR, et al. [Effects of GLP-1 Agonist Exenatide on Cardiac Diastolic Function and Vascular Endothelial Function in Diabetic Patients]. Sichuan Da Xue Xue Bao Yi Xue Ban. 2015;46(4):586-90.
194. Ladeiras-Lopes R, Ferreira-Martins J, Leite-Moreira AF. Acute neurohumoral modulation of diastolic function. Peptides. 2009;30(2):419-25.

195. Tymitz K, Engel A, McDonough S, Hendy MP, Kerlakian G. Changes in Ghrelin Levels Following Bariatric Surgery: Review of the Literature. Obesity Surgery. 2011;21(1):125-30.
196. Shahul S, Rhee J, Hacker Michele R, Gulati G, Mitchell John D, Hess P, et al. Subclinical Left Ventricular Dysfunction in Preeclamptic Women With Preserved Left Ventricular Ejection Fraction. Circulation: Cardiovascular Imaging. 2012;5(6):734-9.
197. Bansal M, Kasliwal RR. How do I do it? Speckle-tracking echocardiography. Indian heart journal. 2013;65(1):117-23.
198. Bijnens BH, Cikes M, Claus P, Sutherland GR. Velocity and deformation imaging for the assessment of myocardial dysfunction. European Journal of Echocardiography. 2009;10(2):216-26.
199. Moors S, van Oostrum NHM, Rabotti C, Long X, Westerhuis MEMH, Kemps HMC, et al. Speckle Tracking Echocardiography in Hypertensive Pregnancy Disorders: A Systematic Review. Obstetrical & Gynecological Survey. 2020;75(8).
200. Ando T, Kaur R, Holmes AA, Brusati A, Fujikura K, Taub CC. Physiological adaptation of the left ventricle during the second and third trimesters of a healthy pregnancy: a speckle tracking echocardiography study. American journal of cardiovascular disease. 2015;5(2):119-26.
201. Koshino Y, Villarraga HR, Somers VK, Miranda WR, Garza CA, Hsiao J-F, et al. Changes in myocardial mechanics in patients with obesity following major weight loss after bariatric surgery. Obesity. 2013;21(6):1111-8.
202. Rodríguez-Flores M, Martin J, Poirier P. Abstract 19564: Short Term Improvement in Subtle Cardiac Dysfunction in Severely Obese Patients After Bariatric Surgery is Not Associated With Changes in Nt-pro-bnp: A Speckle Tracking Study. Circulation. 2015;132(suppl_3):A19564-A.
203. Ashrafian H, le Roux CW. Metabolic surgery and gut hormones - a review of bariatric entero-humoral modulation. Physiol Behav. 2009;97(5):620-31.
204. Chatelain P, Robberecht P, De Neef P, Deschodt-Lanckman M, König W, Christophe J. Secretin and VIP-stimulated adenylate cyclase from rat heart. Pflügers Archiv. 1980;389(1):21-7.
205. Nikolaidis LA, Mankad S, Sokos GG, Miske G, Shah A, Elahi D, et al. Effects of glucagon-like peptide-1 in patients with acute myocardial infarction and left ventricular dysfunction after successful reperfusion. Circulation. 2004;109(8):962-5.
206. Sokos GG, Nikolaidis LA, Mankad S, Elahi D, Shannon RP. Glucagon-like peptide-1 infusion improves left ventricular ejection fraction and functional status in patients with chronic heart failure. J Card Fail. 2006;12(9):694-9.
207. Saravanakumar K, Rao SG, Cooper GM. Obesity and obstetric anaesthesia. Anaesthesia. 2006;61(1):36-48.
208. Blomstrand P, Sjöblom P, Nilsson M, Wijkman M, Engvall M, Länne T, et al. Overweight and obesity impair left ventricular systolic function as measured by left ventricular ejection fraction and global longitudinal strain. Cardiovascular Diabetology. 2018;17(1):113.
209. Rossi RC, Vanderlei LCM, Gonçalves ACCR, Vanderlei FM, Bernardo AFB, Yamada KMH, et al. Impact of obesity on autonomic modulation, heart rate and blood pressure in obese young people. Autonomic Neuroscience. 2015;193:138-41.
210. Buddeberg BS, Fernandes NL, Vorster A, Cupido BJ, Lombard CJ, Swanevelder JL, et al. Cardiac Structure and Function in Morbidly Obese Parturients: An Echocardiographic Study. Anesth Analg. 2018.
211. Lavie CJ, Messerli FH. Cardiovascular Adaptation to Obesity and Hypertension. Chest. 1986;90(2):275-9.

212. Samuelsson A-M, Bollano E, Mobini R, Larsson B-M, Omerovic E, Fu M, et al. Hyperinsulinemia: effect on cardiac mass/function, angiotensin II receptor expression, and insulin signaling pathways. American Journal of Physiology-Heart and Circulatory Physiology. 2006;291(2):H787-H96.
213. Paolisso G, Tagliamonte MR, Galderisi M, Zito GA, D'Errico A, Marfella R, et al. Plasma leptin concentration, insulin sensitivity, and 24-hour ambulatory blood pressure and left ventricular geometry. American Journal of Hypertension. 2001;14(2):114-20.
214. Wong Chiew Y, O'Moore-Sullivan T, Leano R, Byrne N, Beller E, Marwick Thomas H. Alterations of Left Ventricular Myocardial Characteristics Associated With Obesity. Circulation. 2004;110(19):3081-7.
215. Fok WY, Chan LY, Wong JT, Yu CM, Lau TK. Left ventricular diastolic function during normal pregnancy: assessment by spectral tissue Doppler imaging. Ultrasound in Obstetrics & Gynecology. 2006;28(6):789-93.
216. AlJaroudi W, Halley C, Houghtaling P, Agarwal S, Menon V, Rodriguez L, et al. Impact of body mass index on diastolic function in patients with normal left ventricular ejection fraction. Nutrition & Diabetes. 2012;2(8):e39-e.
217. Berkalp B, Cesur V, Corapcioglu D, Erol C, Baskal N. Obesity and left ventricular diastolic dysfunction. International Journal of Cardiology. 1995;52(1):23-6.
218. Ziyrek M, Alpaydın MS. Comparison of myocardial performance index and right ventricular myocardial acceleration during isovolumic contraction in detection of right ventricular dysfunction in obese patients. Turk Kardiyol Dern Ars. 2020;48(6):594-604.
219. Stott D, Bolten M, Salman M, Paraschiv D, Clark K, Kametas NA. Maternal demographics and hemodynamics for the prediction of fetal growth restriction at booking, in pregnancies at high risk for placental insufficiency. Acta Obstet Gynecol Scand. 2016;95(3):329-38.
220. Shin D, Song WO. Prepregnancy body mass index is an independent risk factor for gestational hypertension, gestational diabetes, preterm labor, and small- and large-for-gestational-age infants. The Journal of Maternal-Fetal & Neonatal Medicine. 2015;28(14):1679-86.
221. Walsh SW. Obesity: a risk factor for preeclampsia. Trends in Endocrinology & Metabolism. 2007;18(10):365-70.
222. Lopez-Jaramillo P, Barajas J, Rueda-Quijano SM, Lopez-Lopez C, Felix C. Obesity and Preeclampsia: Common Pathophysiological Mechanisms. Frontiers in Physiology. 2018;9:1838.
223. Khaw A, Kametas NA, Turan OM, Bamfo J, Nicolaides KH. Maternal cardiac function and uterine artery Doppler at 11–14 weeks in the prediction of pre-eclampsia in nulliparous women. BJOG: An International Journal of Obstetrics & Gynaecology. 2008;115(3):369-76.
224. Macdonald-Wallis C, Silverwood RJ, de Stavola BL, Inskip H, Cooper C, Godfrey KM, et al. Antenatal blood pressure for prediction of pre-eclampsia, preterm birth, and small for gestational age babies: development and validation in two general population cohorts. Bmj. 2015;351:h5948.
225. Costa MA. The endocrine function of human placenta: an overview. Reprod Biomed Online. 2016;32(1):14-43.
226. Harrington K, Cooper D, Lees C, Hecher K, Campbell S. Doppler ultrasound of the uterine arteries: the importance of bilateral notching in the prediction of pre-eclampsia, placental abruption or delivery of a small-for-gestational-age baby. Ultrasound Obstet Gynecol. 1996;7(3):182-8.

227. Ghosh GS, Gudmundsson S. Uterine and umbilical artery Doppler are comparable in predicting perinatal outcome of growth-restricted fetuses. BJOG: An International Journal of Obstetrics & Gynaecology. 2009;116(3):424-30.
228. Mone F, McAuliffe FM, Ong S. The clinical application of Doppler ultrasound in obstetrics. The Obstetrician & Gynaecologist. 2015;17(1):13-9.
229. Costa MA. The endocrine function of human placenta: an overview. Reproductive BioMedicine Online. 2016;32(1):14-43.
230. Kirkegaard I, Uldbjerg N, Oxvig C. Biology of pregnancy-associated plasma protein-A in relation to prenatal diagnostics: an overview. Acta Obstet Gynecol Scand. 2010;89(9):1118-25.
231. Cignini P, Maggio Savasta L, Gulino FA, Vitale SG, Mangiafico L, Mesoraca A, et al. Predictive value of pregnancy-associated plasma protein-A (PAPP-A) and free beta-hCG on fetal growth restriction: results of a prospective study. Arch Gynecol Obstet. 2016;293(6):1227-33.
232. Tay J, Masini G, McEniery CM, Giussani DA, Shaw CJ, Wilkinson IB, et al. Uterine and fetal placental Doppler indices are associated with maternal cardiovascular function. American Journal of Obstetrics and Gynecology. 2019;220(1):96.e1-.e8.
233. Masini G, Tay J, McEniery CM, Wilkinson IB, Valensise H, Tiralongo GM, et al. Maternal Cardiovascular Dysfunction is Associated with Hypoxic Cerebral and Umbilical Doppler Changes. Journal of Clinical Medicine. 2020;9(9).
234. Garcia-Gonzalez C, Abdel-Azim S, Galeva S, Georgiopoulos G, Nicolaides KH, Charakida M. Placental function and fetal weight are associated with maternal hemodynamic indices in uncomplicated pregnancies at 35–37 weeks of gestation. American Journal of Obstetrics & Gynecology. 2020;222(6):604.e1-.e10.
235. Dobrowolski P, Kosinski P, Prejbisz A, Szczepkowska A, Klisiewicz A, Januszewicz M, et al. Longitudinal changes in maternal left atrial volume index and uterine artery pulsatility indices in uncomplicated pregnancy. Am J Obstet Gynecol. 2021;224(2):221.e1-.e15.
236. Golinska-Grzybala K, Wiechec M, Golinski B, Rostoff P, Szlósarczyk B, Gackowski A, et al. Subclinical cardiac performance in obese and overweight women as a potential risk factor of preeclampsia. Pregnancy Hypertension. 2021;23:131-5.
237. Teulings NEWD, Wood AM, Sovio U, Ozanne SE, Smith GCS, Aiken CE. Independent influences of maternal obesity and fetal sex on maternal cardiovascular adaptation to pregnancy: a prospective cohort study. International Journal of Obesity. 2020;44(11):2246-55.
238. Gaillard R, Arends LR, Steegers EA, Hofman A, Jaddoe VW. Second- and third-trimester placental hemodynamics and the risks of pregnancy complications: the Generation R Study. Am J Epidemiol. 2013;177(8):743-54.
239. Atkins K, Boyd C, Kasdaglis T, Baschat A, Harman C. 391: Are obesity and uterine artery vascular resistance directly related? American Journal of Obstetrics & Gynecology. 2013;208(1):S172-S3.
240. Aksoy AN NT, Gozgec EG. The relationship between body mass index in late pregnancy and fetomaternal blood flow parameters: A
prospective cross-sectional study. Annals of Medical Research. 2019
241. Vasapollo B, Valensise H, Novelli GP, Altomare F, Galante A, Arduini D. Abnormal maternal cardiac function precedes the clinical manifestation of fetal growth restriction. Ultrasound in Obstetrics & Gynecology. 2004;24(1):23-9.
242. Patil M, Panchanadikar TM, Wagh G. Variation of Papp-A Level in the First Trimester of Pregnancy and Its Clinical Outcome. The Journal of Obstetrics and Gynecology of India. 2014;64(2):116-9.

243. Goel A, Maski Manish R, Bajracharya S, Wenger Julia B, Zhang D, Salahuddin S, et al. Epidemiology and Mechanisms of De Novo and Persistent Hypertension in the Postpartum Period. Circulation. 2015;132(18):1726-33.
244. Verlohren S, Melchiorre K, Khalil A, Thilaganathan B. Uterine artery Doppler, birth weight and timing of onset of pre-eclampsia: providing insights into the dual etiology of late-onset pre-eclampsia. Ultrasound in Obstetrics & Gynecology. 2014;44(3):293-8.
245. Melchiorre K, Wormald B, Leslie K, Bhide A, Thilaganathan B. First-trimester uterine artery Doppler indices in term and preterm pre-eclampsia. Ultrasound in Obstetrics & Gynecology. 2008;32(2):133-7.
246. Gómez O, Figueras F, Fernández S, Bennasar M, Martínez JM, Puerto B, et al. Reference ranges for uterine artery mean pulsatility index at 11–41 weeks of gestation. Ultrasound in Obstetrics & Gynecology. 2008;32(2):128-32.
247. NHS Digital. Statistics on Obesity, Physical Activity and Diet 2020: Data tables. NHS Digital. May 2020. [Statistics on Obesity, Physical Activity and Diet, England, 2020 - NHS Digital (Accessed Jul 2021)
248. Blüher M. Obesity: global epidemiology and pathogenesis. Nat Rev Endocrinol. 2019;15(5):288-98.
249. Apovian CM, Aronne LJ, Bessesen DH, McDonnell ME, Murad MH, Pagotto U, et al. Pharmacological management of obesity: an endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2015;100(2):342-62.
250. Christinajoice S, Misra S, Bhattacharya S, Kumar SS, Nandhini BD, Palanivelu C, et al. Impact of Bariatric Surgery on Female Reproductive Health and Maternal Outcomes. Obes Surg. 2020;30(2):383-90.
251. ACOG practice bulletin no. 105: bariatric surgery and pregnancy. Obstet Gynecol. 2009;113(6):1405-13.
252. Karmon A, Sheiner E. Timing of gestation after bariatric surgery: should women delay pregnancy for at least 1 postoperative year? Am J Perinatol. 2008;25(6):331-3.
253. Rottenstreich A, Levin G, Kleinstern G, Rottenstreich M, Elchalal U, Elazary R. The effect of surgery-to-conception interval on pregnancy outcomes after sleeve gastrectomy. Surg Obes Relat Dis. 2018;14(12):1795-803.
254. Rasteiro C, Araújo C, Cunha S, Caldas R, Mesquita J, Seixas A, et al. Influence of Time Interval from Bariatric Surgery to Conception on Pregnancy and Perinatal Outcomes. Obes Surg. 2018;28(11):3559-66.
255. Tan MY, Syngelaki A, Poon LC, Rolnik DL, O'Gorman N, Delgado JL, et al. Screening for pre-eclampsia by maternal factors and biomarkers at 11-13 weeks' gestation. Ultrasound Obstet Gynecol. 2018;52(2):186-95.
256. Savvidou M, Nelson SM, Makgoba M, Messow CM, Sattar N, Nicolaides K. First-trimester prediction of gestational diabetes mellitus: examining the potential of combining maternal characteristics and laboratory measures. Diabetes. 2010;59(12):3017-22.
257. Beta J, Akolekar R, Ventura W, Syngelaki A, Nicolaides KH. Prediction of spontaneous preterm delivery from maternal factors, obstetric history and placental perfusion and function at 11–13 weeks. Prenatal Diagnosis. 2011;31(1):75-83.
258. Frick AP, Syngelaki A, Zheng M, Poon LC, Nicolaides KH. Prediction of large-for-gestational-age neonates: screening by maternal factors and biomarkers in the three trimesters of pregnancy. Ultrasound in Obstetrics & Gynecology. 2016;47(3):332-9.
259. Papastefanou I, Wright D, Nicolaides KH. Competing-risks model for prediction of small-for-gestational-age neonate from maternal characteristics and medical history. Ultrasound Obstet Gynecol. 2020;56(2):196-205.
260. Snijders RJ, Nicolaides KH. Fetal biometry at 14-40 weeks' gestation. Ultrasound Obstet Gynecol. 1994;4(1):34-48.

261. Ashrafian H, Bueter M, Ahmed K, Suliman A, Bloom SR, Darzi A, et al. Metabolic surgery: an evolution through bariatric animal models. Obes Rev. 2010;11(12):907-20.
262. Guijarro A, Kirchner H, Meguid MM. Catabolic effects of gastric bypass in a diet-induced obese rat model. Curr Opin Clin Nutr Metab Care. 2006;9(4):423-35.
263. Eaton M, Davies AH, Devine J, Zhao X, Simmons DG, Maríusdóttir E, et al. Complex patterns of cell growth in the placenta in normal pregnancy and as adaptations to maternal diet restriction. PLoS One. 2020;15(1):e0226735.
264. Roberts VHJ, Lo JO, Lewandowski KS, Blundell P, Grove KL, Kroenke CD, et al. Adverse Placental Perfusion and Pregnancy Outcomes in a New Nonhuman Primate Model of Gestational Protein Restriction. Reprod Sci. 2018;25(1):110-9.
265. Wallace JM, Bhattacharya S, Campbell DM, Horgan GW. Inter-Pregnancy Weight Change and the Risk of Recurrent Pregnancy Complications. PLoS One. 2016;11(5):e0154812.
266. Jain AP, Gavard JA, Rice JJ, Catanzaro RB, Artal R, Hopkins SA. The impact of interpregnancy weight change on birthweight in obese women. American Journal of Obstetrics and Gynecology. 2013;208(3):205.e1-.e7.
267. Rottenstreich A, Levin G, Ben Porat T, Rottenstreich M, Meyer R, Elazary R. Extremely early pregnancy (<6 mo) after sleeve gastrectomy: maternal and perinatal outcomes. Surgery for Obesity and Related Diseases. 2021;17(2):356-62.
268. Kirkpatrick JN, Vannan MA, Narula J, Lang RM. Echocardiography in Heart Failure: Applications, Utility, and New Horizons. Journal of the American College of Cardiology. 2007;50(5):381-96.
269. Huang SJ, McLean AS. Appreciating the Strengths and Weaknesses of Transthoracic Echocardiography in Hemodynamic Assessments. Cardiology Research and Practice. 2012;2012:894308.
270. Alfakih K, Reid S, Jones T, Sivananthan M. Assessment of ventricular function and mass by cardiac magnetic resonance imaging. European Radiology. 2004;14(10):1813-22.
271. Chatterjee K. The Swan-Ganz catheters: past, present, and future. A viewpoint. Circulation. 2009;119(1):147-52.
272. Manda YR, Baradhi KM. Cardiac Catheterization Risks and Complications. StatPearls. Treasure Island (FL): StatPearls Publishing

Appendix 1

Studies of cardiovascular changes after bariatric surgery

	Title and Author	Meta-analysis	Results and conclusion
1	The Effects of Bariatric Surgery on Cardiac Structure and Function: a Systematic Review of Cardiac Imaging Outcomes. Aggarwal el al. 2016	N=1486 40 studies pre and post-surgery Follow up 3-45months	LV mass ↓ LV mass index ↓ LV end-diastolic volume ↓ LA diameter ↓ LV EF improvement (1.198%, 95%CI -0.050-2.347) E/A ratio improved BMI ↓ 13.51 points post-surgery from a baseline of 47.2 kg/m^2
2	Effects of bariatric surgery on cardiac structure and function: a systematic review and meta-analysis. Cuspidi et al. 2016	N= 1,022 23 studies pre and post-surgery Follow up 3-45months	LV mass ↓ LV mass indexed to height ↓ Relative wall thickness ↓ E/A ratio improved LA diameter ↓ LV EF no change (10 studies N=600 subjects) BMI ↓ pre-surgery 39 to 60 kg/m^2 to post-surgery 29 to 40 kg/m^2
3	Bariatric surgery and cardiovascular outcomes: a systematic review. Vest et al. 2012	N=19 543 73 studies Echo data N=713 Follow up 3-176.4 months	Hypertension ↓ in 63% Diabetes ↓ in 73% Hyperlipidaemia ↓ in 65%. LVM ↓ LA diameter and LV diastolic dimension ↓ E/A ratio improved LVEF no change (471 patients without a HF diagnosis) BMI ↓ pre-surgery 48.7 kg/m^2 to 31.6 kg/m^2 post-surgery.
4	Effect of bariatric surgery on cardiovascular risk profile. Heneghan et al. 2011	N= 16 867 52 studies Follow up 2-155m	Hypertension ↓ in 68% Diabetes ↓ in 75% Dyslipidaemia ↓ in 71%. Systolic BP ↓ from 139 to 124 mm Hg, Diastolic BP from 87 to 77 mm Hg. 40% relative risk ↓ for 10-year coronary heart disease risk (determined by the Framingham risk score).

5	Effects of bariatric surgery on RV structure and function. Cuspidi et al. 2014	Systematic review N=537 8 studies pre and post-surgery. Follow up 4.5-45m	RV mass ↓ (on MRI but no association with function) RV Myocardial performance index, Fractional area change ↑ RV global longitudinal strain ↑ LV mass and volume ↓ BMI ↓pre-surgery 37 to 51 kg/m^2 to post-surgery 29.9 to 37 kg/m^2
	Large studies	**Method**	**Results**
1	Favourable changes in cardiac geometry and function following gastric bypass surgery: 2-year follow-up in the Utah obesity study Owan et al. Feb 2011	N= 423 Pre surgery a post-surgery. Follow up 2 years	LV wall thickness, relative wall thickness ↓ Interventricular septum thickness ↓ LV mass index ↓ LV diastolic and systolic volumes, no change Function: LV endocardial fractional shortening, LV EF, no change Midwall fractional shortening ↑ RV Fractional area change ↑ E/E' slightly improved BMI ↓ -15.4 points post-surgery
2	Ventricular remodeling post-bariatric surgery: is the type of surgery relevant? A prospective study with 3D speckle tracking. Kaier et al. 2014	N=52 Pre surgery a post-surgery. Follow up 6 months 18 laparoscopic sleeve gastrectomy 34 laparoscopic gastric bypass	3D speckle tracking LV EF ↑ pre-surgery: 59+8% vs. post-surgery: 67+7% RV EF ↑ surgery: 60+9% vs. post-surgery: 68+8.2% LV mass ↓ RV mass ↓ Global RV strain ↑ Global LV strain ↑ Sleeve gastrectomy and gastric bypass had comparable effects.
3	Effects of bariatric surgery on cardiac remodelling: Clinical and pathophysiologic implications Author(s): Graziani et al. 2013	N=52 Pre surgery a post-surgery. Follow up 2 year	LV wall thickness and mass ↓ LV end-diastolic and end-systolic volumes ↓ LV EF ↑ (from 55.9+/4.8 to 59.2+/-4.4%). E/A ratio slight improvement
4	The impact of bariatric surgery on renal and cardiac functions in morbidly obese patients. Luaces et al 2012	N=61 Pre surgery a post-surgery. Follow up 1 year	Hypertension ↓ incidence 69% Dyslipidaemia ↓ incidence 73% Diabetes ↓ incidence 68% LV mass index, relative wall thickness ↓

			Diastolic function no change
5	The Effect of Surgical Weight ↓ on Left Ventricular Structure and Function in Severe Obesity Hsuan et al. 2012	N=66 Pre surgery a post-surgery. Follow up 3 months	LV wall thickness, relative wall thickness, septal thickness ↓ LV mass, and LV mass index ↓ Function: LV fractional shortening no change Peak systolic mitral annular velocity ↑ E/A ratio improvement
6	Structural and Functional Changes in Left and Right Ventricles After Major Weight Loss Following Bariatric Surgery for Morbid Obesity Graza 2010	N= 57 Pre surgery a post-surgery. Follow up 3.7 years	Posterior wall thickness, septal thickness LV mass and LV mass index ↓ LV EF, Myocardial performance index, no change RV Myocardial performance index, no change
7	Weight loss after bariatric surgery improves aortic elastic properties and left ventricular function in individuals with morbid obesity: a 3-year follow-up study. Ikonomidis et al. 2007	N= 60 Pre surgery a post-surgery. Follow up 36 months	LV diastolic diameter and volume ↓ LV mass and wall thickness ↓ Diastolic function ↑
8	Impact of obesity and surgical weight ↓ on cardiac remodelling Mostfa et al. 2018	N= 52 Pre surgery a post-surgery. Follow up 6 months	LV mass index ↓ LV end systolic volume and LV end diastolic volume ↑ EF ↑ from 59 +/- 8 to 67 +/- 7 $p < 0.001$ LV and RV longitudinal systolic strain ↑ RV function: Fraction area change, Tricuspid annular plane systolic exertion non-significant ↑
9	The Effect of Weight Loss on the Cardiac Structure and Function After Laparoscopic Adjustable Gastric Banding Surgery in Morbidly Obese Individuals Dzenkeviciūte et al. 2014	N= 83 Pre surgery a post-surgery. Follow up 12 months	LV end-diastolic diameter ↓ LV mass, LV mass index ↓ LV geometry or LV hypertrophy subtypes, no change E/A ratio ↓ E wave deceleration time, E/E' ↓ Overall diastolic dysfunction, no change BMI ↓ pre-surgery 46.9 kg/m^2 to 40.1 kg/m^2 LV mass associated with weight loss, not change in blood pressure or metabolic parameters

Appendix 2.

Studies of hypertensive disorders in pregnancy after bariatric surgery

Title and Author	Study and methods	Results and conclusion
Maternal and neonatal outcomes after bariatric surgery; a systematic review and meta-analysis: do the benefits outweigh the risks? Kwong et al.	Meta-analysis 20 studies BS= 686 C=584 pre-surgery and pre-pregnancy BMI	Control: pre-surgery BMI BS: GH ↓ (OR, 0.38; 95% CI, 0.19-0.76; number needed to benefit, 11) All hypertensive disorders ↓ (OR, 0.38; 95% CI, 0.27-0.53; number needed to benefit, 8) Control: pre-pregnancy BMI BS: PE no difference
Maternal and neonatal outcomes in women undergoing bariatric surgery: a systematic review and meta-analysis. Galazis et al.	Meta-analysis 17 studies BS= 5361 C= 160,773 in multiple groups	Control: Total meta-analysis, BS: ↓ (P=0.007) Control: obese women before or no surgery, BS= no difference PE Control: same women before and after BS, BS: PE ↓ Control: different women after and before BS, BS: PE ↓ Control: pre-pregnancy BMI, BS: no difference (P=0.08) Control: pre-surgery BMI, BS: no difference Control: obese women with no BS, LAGB: PE ↓
Maternal and neonatal outcome after laparoscopic adjustable gastric banding: a systematic review. Vrebosch et al.	Systematic review 4 studies with control group BS =285 C= 1614 obese 7 without a control group BS= 477	Control: same women before and after BS, obese women, normal weight women BS: PIH and PE ↓compared to obese but higher than in normal weight without surgery
A meta-analysis of maternal and fetal outcomes of pregnancy after bariatric surgery Yi et al.	Meta-analysis Nine studies BS =1350 C=3843 obese	BS: hypertensive disorders ↓ (OR 0.42, 95% CI 0.23–0.78; I^2 = 83.3%, P < 0.001)
Pregnancy and fertility following bariatric surgery: a systematic review. Maggard et al.	Systematic review 13 studies	BS: hypertensive disease ↓

Obstetrical and neonatal outcomes in women following gastric bypass: a Danish national cohort study. Berlac et al.	B=415 C= 827 matched pre-pregnancy BMI C=829 normal BMI	Control: pre-pregnancy BMI, BS: PE ↓ (3.9% vs 5.6% in control, P<0001) Control: normal BMI, BS: no significant difference (3.9% vs 2.2% normal BMI)
Maternal and neonatal outcomes for pregnancies before and after gastric bypass surgery. Adams et al.	BS= 295 C =295 pre-surgery BMI	BS: PIH↓ (OR 0.31, 95% CI 0.14–0.65; P=0.0009)
Impact of bariatric surgery on hypertensive disorders in pregnancy: retrospective analysis of insurance claims data. Bennett et al.	BS= 316 C= 269 delivered before surgery	BS: PE and eclampsia ↓ (OR 0.20, 95% CI 0.09 to 0.44), Chronic hypertension ↓ (OR 0.39, 0.20 to 0.74) GH ↓ (OR 0.16, 0.07 to 0.37)
Downsizing pregnancy complications: A study of paired pregnancy outcomes before and after bariatric surgery Aricha-Tamir et al.	BS= 288 paired pregnancies 144 deliveries before 144 after bariatric surgery.	BS: hypertensive disorders ↓ (31.9% versus 16.6%; P =.004)
Effect of bariatric surgery on pregnancy outcome Weintraub et al.	BS=507 C= 301 different women who went on to have BS	BS: hypertensive disorders ↓ (23.6% vs 11.2%; P < 0.001)
Birth outcomes in obese women after laparoscopic adjustable gastric banding Dixon et al.	BS=79 C= 40 same woman pre-surgery pregnancy C=79 obese	Control: same women before BS, BS: PIH and PE ↓ (10% and 5% vs 45% and 28% in penultimate pregnancy, P=<0.05) Control: obese, BS: PIH and PE ↓ (10% and 5% vs 38% and 25% in obese group, P=<0.05) Comparable with community levels (12%, cohort=1382)
Pregnancy outcome in morbidly obese women before and after laparoscopic gastric banding. Lapolla et al.	BS=69 C=120 obese C=858 non-obese	BS: GH ↓ (9.6% vs obese group 23.5%, P< 0.05) PE ↓ (12.0% vs obese group 20.8%, P< 0.05) GH ↑ (9.6% vs normal group 2.4%, P< 0.05) PE ↑ (12.0% vs normal group 2.3%, P< 0.001)
Obstetrical and Neonatal Outcomes of Pregnancies following Gastric Bypass Surgery: A Retrospective Cohort Study in a French Referral Centre.	BS 24 C=120 matched pre-pregnancy BMI C=120 normal BMI	PIH or PE no significant difference

Santulli et al.		
Obstetric outcome following laparoscopic adjustable gastric banding Ducareme et al.	BS=13 C= 414 matched pre-pregnancy BMI	BS: ↓ PE (0% vs 3.1% in obese P<0.05), PIH (7.7% vs 8.2%, non-significant)