Impaired Maternal Hemodynamics in Morbidly Obese Women: A Case-Control Study

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ABSTRACT

Aim: Maternal obesity is associated with significant pregnancy complications and is a risk factor for the development of hypertensive disorders of pregnancy as well as other adverse outcomes. There are few data regarding the hemodynamic aberrations observed in maternal obesity. The aim of this study was to investigate maternal hemodynamics in morbidly obese pregnant women.

Methods: This was a prospective, case-control study of morbidly obese women (BMI >40kg/m^2) and controls (BMI 20-29.9 kg/m^2) at a ratio of one-to-ten. The control population was matched for maternal age and gestational age. BMI was calculated based on maternal

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height and weight at the time of recruitment to the study, which occurred on the same day as the hemodynamic assessment. Pregnant women in the second or third trimester of pregnancy were included. Women who were found to be hypertensive at any time were excluded from the study. USCOM-1A® was used to assess hemodynamic parameters (heart rate, stroke volume, cardiac output and systemic vascular resistance). The parameters were corrected for body surface area (BSA) to provide the stroke volume index (SVI), cardiac index (CI) and systemic vascular resistance index (SVRI). Mann Whitney-U test was used to compare the medians of the hemodynamic variables between the two groups.

Results: A total of 30 obese women and 327 controls were recruited. There was no difference in maternal (p=0.506) or gestational (p=0.693) age at recruitment between the groups. Mean arterial pressure was higher both at pregnancy booking (90 vs 80 mmHg, p<0.001) and study recruitment (91 vs 85 mmHg, p<0.001) in the obese group. Heart rate was higher in the obese group (p=0.003), however there was no difference in stroke volume (p=0.271), cardiac output (p=0.238) or systemic vascular resistance (p=0.635). Following correction of these parameters for BSA, the SVI (34 vs 45 ml/m^2, p<0.001) and CI (2.96 vs 3.64 L/min/m^2, p<0.001) were significantly reduced in the obese group, whilst the SVRI was significantly higher (2354 vs 1840 dynes-sec-cm^5/m^2, p<0.001).

Conclusion: The findings of our study suggest that cardiac function is significantly altered in morbidly obese pregnant women. In order to make appropriate comparisons between individuals, it is imperative that hemodynamic parameters are indexed for BSA – as indeed they are in pediatric cardiology. The novel finding of a reduced CI in morbidly obese pregnant women may explain the predisposition to preeclampsia and other adverse outcomes in this population and warrants further investigation.

INTRODUCTION

Obesity is an epidemic, which is associated with heightened perinatal mortality and morbidity (1, 2). In the developed world, its prevalence is reaching unprecedented levels. In 2013, 19% of women of childbearing age in England were obese, a significant increase from the reported prevalence of 12% in 1993 (3). There is a considerable body of evidence that links maternal obesity to a higher risk of adverse pregnancy outcomes, including hypertensive disorders of pregnancy, diabetes, pregnancy loss, intrapartum complications and maternal death (2, 4-6).

Normal physiological adaptation to pregnancy includes an increase in heart rate (HR) and cardiac output (CO) and a decrease in mean arterial pressure (MAP) and systemic vascular resistance (SVR). Structurally, there is significant cardiac remodeling with an increase in left ventricular wall mass and chamber size (7). Maternal obesity is associated with increased sympathetic activation resulting in an increase in heart rate, myocardial contractility and vasoconstriction, which in turn leads to a raised MAP and SVR. Endothelial cell dysfunction caused by the release of pro-inflammatory mediators by adipose tissue is a contributory factor to the cardiovascular complications associated with obesity.

Despite the significant health and economic impact of maternal obesity, there is a paucity of good quality studies assessing central hemodynamic parameters in morbidly obese pregnant women. The results of published studies have been conflicting with most including small sample sizes (8, 9). One reason for this has been the limitation of validated, non-invasive tools that can be reliably and safely employed to investigate maternal hemodynamics. Using invasive methods, such as thermodilution via a pulmonary artery catheter would be neither ethically, nor practically feasible in an obstetric population.

The majority of published data regarding maternal hemodynamics in morbidly obese pregnant women has been using echocardiography, which has been regarded as the widely accepted, non-invasive method of choice in the obstetric population. There are no published studies in the literature investigating maternal hemodynamics in morbidly obese pregnant women using non-invasive methods, other than echocardiography. The main aim of this study was to investigate maternal hemodynamics in morbidly obese pregnant women.

METHODS

Study population and recruitment

This was a prospective, case-control study of 30 morbidly obese pregnant women and 327 controls. Obesity was defined as a body mass index (BMI) greater than 30kg/m^2. Obesity is subdivided into classes I (BMI 30-34.9 kg/m^2), II (BMI 35-39.9 kg/m^2) and III (BMI ≥40 kg/m^2) (1,2,6,7). Morbid obesity is defined as BMI ≥40 kg/m^2 (1,2,7). The controls had a BMI between 20-29.9 kg/m^2. The control population was matched for maternal age and gestational age. We attempted to recruit 10 controls for each obese case (ratio of 1:10). Women aged 16 and over with singleton pregnancies were recruited from routine antenatal scanning clinics and maternity day assessment unit at our tertiary centre. Women who were found to be hypertensive at the time of study recruitment, had a pre-existing diagnosis of hypertensive disorders of pregnancy (ISSHP 2014) or congenital / acquired heart disease, were excluded from the study. Written consent was obtained from all study participants and research ethics committee approval (12/LO/0810) was obtained prior to performing the study investigations. Pregnant women in the second or third trimester of pregnancy were invited to participate.

All non-invasive assessments were performed in the same room, under standardized conditions for the entire cohort. Maternal height and weight were obtained at study recruitment and used to calculate maternal BMI. Following a five-minute period of physical inactivity where a medical history was obtained, USCOM-1A® measurements were obtained. Subjects in the first and early second trimester (before 20 weeks' gestation) were assessed in a supine position, while those in the late second trimester (after 20 weeks' gestation) and third trimester were in a left lateral position. USCOM-1A® was employed in the flow tracer mode (automated tracing of each Doppler profile). For each patient, one Doppler acquisition containing a minimum of two Doppler profiles was used for analysis. Measurements were obtained on one occasion for each subject. One investigator assessed the quality of each Doppler acquisition prior to analysis. If Doppler profiles were deemed to be unsuitable for analysis then they were removed, eg noise artefact from valve closure. All researchers received formal training on the correct use of the USCOM-1A® device and performed a minimum number of training cases prior to study recruitment.

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Research Investigations

Maternal height, weight and blood pressure were obtained prior to hemodynamic assessment. Blood pressure was obtained using an upper arm automatic blood pressure

(BP) monitor (Microlife, Microlife AG Swiss Corporation, Switzerland), in a semi-recumbent position and using an appropriate sized cuff. USCOM-1A® utilizes continuous wave Doppler, with a non-imaging probe in the suprasternal notch to obtain velocity time integrals (VTI) of transaortic blood flow at the left ventricular outflow tract. Using an anthropometric algorithm, which correlates the outflow tract diameter with the patient's given height, USCOM-1A® uses the VTIs to compute stroke volume (SV) and therefore CO and produce a complete hemodynamic profile, including HR, SV, CO and SVR. Each Doppler acquisition used for analysis had a minimum of 2 consecutive Doppler profiles (cardiac cycles). Acquisitions with the least amount of interference and the best quality VTIs, deemed by the study investigator to best represent transaortic blood flow, were obtained in the device's flowtracer mode. By calculating the body surface area (BSA) using examination weight and height, USCOM-1A® calculates the indexed hemodynamic variable corrected for BSA. The parameters examined include cardiac index (CI), stroke volume index (SVI) and SVR index (SVRI).

Statistical Analysis

Categorical data were presented as number and percentage, while continuous data were presented as the median and interquartile range (IQR). Continuous data were examined using the Shapiro-Wilk test to assess the distribution of data. Chi-Square test, or Fisher's exact test when appropriate, was used to compare the categorical variables. Mann Whitney-U test was used to compare the medians of the hemodynamic variables between the two groups. A p-value less than 0.05 was deemed statistically significant. All statistical analysis was carried out using IBM SPSS Statistics version 21 (IBM Corporation, Armonk, New York, United States).

RESULTS

A total of 30 women with class 3 maternal obesity were recruited to this study. Seven patients were excluded, due to hypertensive disorders of pregnancy (n=5) and poor quality USCOM-1A® Doppler acquisitions (n=2). Therefore, a total of 23 cases were included in the final analysis. The control group consisted of 327 women. Patients were recruited between September 2012 and April 2016. The median gestational age at study recruitment for both groups was 31 weeks. The baseline demographic characteristics and pregnancy outcomes of the two groups are displayed in Table 1. A summary of the analysis of the hemodynamic variables is shown in Table 2.

There was no difference in maternal age (p=0.506) or gestational age at recruitment (p=0.693) between the groups. There was a significant difference in the proportion of

Afrocaribbean and Caucasian patients between the obese and control study groups. Although differences in hemodynamic parameters between the study groups may be attributed to ethnicity, we have shown previously in a much larger prospective study that ethnicity does not affect maternal hemodynamic parameters (UOG-2016-0728, in press). The MAP was significantly higher, both at booking (90 vs 80 mmHg, p<0.001) and at the study recruitment (91 vs 85 mmHg, p<0.001) in the obese group. The examination weight (113 vs 70 kg, p<0.001) and BMI (41.3 vs 25.9 kg/m^2, p<0.001) were significantly higher in the obese group.

Hemodynamic parameters

The BSA was unsurprisingly significantly higher in the obese group (p<0.001). Heart rate was also higher in the obese group (p=0.003). We found no significant difference between SV (p=0.271), CO (p=0.238) or SVR (p=0.635) between the two groups. Following correction of the variables for BSA, the SVI (p<0.001) and CI (p<0.001) were significantly reduced in the obese group when compared to the control group (Figures 1-2, Table 2). We also found a higher SVRI in the obese group (p<0.001) (Figure 3, Table 2).

DISCUSSION

Summary of study findings

Morbidly obese pregnant women had significantly higher HR, but there was no difference in SV, CO or SVR when compared to the control group. Importantly, once corrected for BSA, we found that morbidly obese pregnant women had a significantly lower SVI and CI than the control group. We also demonstrated that the obese group had a significantly higher SVRI than the control group.

Interpretation of study findings and comparison with the literature

Our work suggests an impaired cardiac function in morbidly obese pregnant women when compared to non-obese controls. Our work also highlights the importance of correcting for BSA when comparing individuals with a wide range of body shapes and sizes – as indeed is standard practice in pediatric cardiology.

Dennis *et al.* (9) used transthoracic echocardiography to assess the cardiovascular changes in a sample of 15 obese women (BMI >30 kg/m^2). When compared to a cohort of 40 women with a normal BMI, the authors reported no difference in HR, SV, SVR or CO. However, they did report an increased left ventricular mass in the obese group. Interestingly, the authors did not correct the hemodynamic parameters for BSA. Previous work by Veille (8),

investigated eight morbidly obese pregnant women using M-mode echocardiography, but showed no difference in CO, or left ventricular function. In agreement with other studies (10, 11), we found a significantly higher MAP and HR in our obese group.

Due to growing interest in non-invasive CO monitoring technology, there have been many advances in different modalities within this field. Several non-invasive monitors are commercially available, using various techniques such as ultrasound, bioimpedance and bioreactance. Our group (12) has shown that USCOM-1A® is a reproducible and repeatable device. When assessed against a standard of 2-d transthoracic echocardiography, USCOM-1A® meets the critical level of a 30% mean percentage difference between two CO methodologies, in the third trimester of pregnancy. Our previous work highlights that USCOM-1A® can be used as a clinically acceptable alternative to echocardiography in advanced pregnancy. Its benefits include the ease with which a hemodynamic profile can be obtained, as compared to conventional echocardiography.

Study limitations and strengths

The strengths of this study included its novel data, relatively large sample size when compared to other published studies, excluding patients that developed adverse pregnancy outcomes eliminating the independent bias of these factors on maternal hemodynamics. A limitation of this study is that we did not include a non-pregnant morbidly obese group. This group could have provided data on the cardiac function in obese women outside of pregnancy, and therefore allowed us to evaluate whether cardiac impairment occurs independently of, or as a result of, pregnancy.

Clinical and research implications

Our work suggests that cardiac function is altered in morbidly obese pregnant women. We highlight the need to index hemodynamic variables for BSA in order to make appropriate comparisons between individuals with a diverse range of anthropometric parameters. Our work demonstrates an adverse cardiovascular profile exhibited by obese pregnant women, which would support why obesity is a risk factor for maternal cardiovascular disorders (13, 14).

We believe that the increasing prevalence of maternal obesity is a sufficient cause for concern to warrant the attention of future research. The current study, whilst suggesting an impaired cardiac function, is unable to elucidate structural or functional differences. A reduced CI in maternal obesity could be attributable to a number of pathways, including diastolic or systolic dysfunction or hypertrophic changes (14, 15). These changes could be assessed using echocardiography. Future work should aim to assess whether cardiac impairment has a relationship to the amount of weight gained, and therefore extra demand

on the cardiovascular system, during the pregnancy. Moreover, prospective large studies are needed to determine whether cardiac impairment pre-dates the pregnancy, or occurs as a result of the cardiovascular maladaptation to the significant demands of an ongoing pregnancy. In order to address these important questions, longitudinal assessment is required, both pre-pregnancy and in obese non-pregnant women.

Conclusion

Our results demonstrate a reduced SVI and CI, and a higher SVRI in morbid maternal obesity. Assessing absolute values without correcting for BSA, does not allow for appropriate comparison in an obstetric population, especially in the context of obesity. The methodology used in this study has been previously validated and appears to have many positive features enabling its use in future clinical and research work. The novel finding of a reduced CI in morbidly obese pregnant women may explain the predisposition to preeclampsia and other adverse outcomes in this population (13-15). As impaired maternal hemodynamics in morbid obesity may not necessarily correlate with cardiac dysfunction, further investigation using alternate methodologies to carry out an in-depth assessment of structural and functional changes associated with maternal obesity is warranted.

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Table 1. Baseline characteristics and birth outcomes of the study groups.

	Morbidly Obese pregnant women (n=23)	**Controls (n=327)**	**p value**
Maternal Age in years, median (IQR)	31 (27-35)	32 (28-38)	0.506
Gestational age in weeks, median (IQR)	31.5 (27.8-35.1)	31.1 (27.6-34.4)	0.693
Ethnicity, n (%)			
Caucasian	9 (39)	228 (69)	**0.002**
Afrocaribbean	9 (39)	33 (10)	**0.001**
Asian	3 (13)	55 (17)	0.779
Mixed / Other	2 (9)	11 (3)	0.207
Assisted Conception, n (%)	0 (0)	14 (4)	0.611
Nulliparity, n (%)	9 (39)	187 (57)	0.092
Maternal weight at pregnancy booking in kilograms, median (IQR)	104 (93-118)	61.5 (56-70)	**<0.001**
Maternal weight at the assessment in kilograms, median (IQR)	113 (103-117)	70 (64-76)	**<0.001**
Maternal BMI at the hemodynamic assessment in kilograms/ m^2, median (IQR)	41.3 (40.8-42.9)	25.9 (24.2-27.7)	**<0.001**
Mode of Delivery, n (%)			
Spontaneous vaginal	13 (56)	183 (58)	0.883
Operative vaginal	2 (9)	61 (19)	0.205
Caesarean Section	8 (35)	73 (23)	0.208
Preterm delivery (<37 weeks), n (%)	1 (4)	8 (2.5)	0.603
Gestational age at delivery, median	40.3 (37.4-41.5)	40.2 (37.6-41.6)	0.813
Birthweight in grams, median (IQR)	3470 (3070-3650)	3320 (3100-3624)	0.716

Table 2. Maternal non-invasive hemodynamic assessment in the study groups

	Morbidly Obese pregnant women (n=23)	**Controls (n=327)**	**p value**
Maternal mean arterial pressure at pregnancy booking in mmHg, median (IQR)	90 (83-97)	80 (74-86)	**<0.001**
Maternal mean arterial pressure at the hemodynamic assessment in mmHg, median (IQR)	91 (86-96)	85 (79-91)	**<0.001**
Body Surface Area in m^2, median (IQR)	2.36 (2.23-2.41)	1.82 (1.73-1.91)	**<0.001**
Heart rate in bpm, median (IQR)	91 (82-101)	82 (73-93)	**0.003**
Stroke volume in mls, median (IQR)	79 (67-89)	82 (71-93)	0.271
Stroke Volume Index in mls/m^2, median (IQR)	34 (30-37)	45 (39-51)	**<0.001**
Cardiac Output in L/min, median (IQR)	7.13 (6.20-7.70)	6.60 (5.80-7.55)	0.238
Cardiac Index in L/min/m^2, median (IQR)	2.96 (2.72-3.30)	3.64 (3.19-4.16)	**<0.001**
Systemic Vascular Resistance in dynes-sec-cm^5, median (IQR)	1016 (886-1176)	1032 (890-1170)	0.635
Systemic Vascular Resistance Index in dynes-sec-cm^5/m^2, median (IQR)	2354 (2136-2828)	1840 (1601-2145)	**<0.001**

FIGURE LEGENDS

Figure 1. Box and whisker plot of the stroke volume index in the two study groups. The horizontal line in the box represents the median, the box represents the interquartile range and the whiskers indicate the minimum and maximum values.

Figure 2. Box and whisker plot of the cardiac index in the two study groups. The horizontal line in the box represents the median, the box represents the interquartile range and the whiskers indicate the minimum and maximum values.

Figure 3. Box and whisker plot of the systemic vascular resistance index in the two study groups. The horizontal line in the box represents the median, the box represents the interquartile range and the whiskers indicate the minimum and maximum values.