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MATERNAL ECHOCARDIOGRAPHIC CHANGES IN TWIN PREGNANCIES WITH AND WITHOUT PRE-ECLAMPSIA

Short title: Maternal cardiovascular system in twin pregnancy

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CONTRIBUTION

What are the novel findings of this work?

Twin pregnancies demonstrated cardiac changes in left ventricular mass and indices of diastolic function comparable to singleton pregnancy complicated by hypertensive disorders of pregnancy (HDP). Cardiac maladaptation in twins became further exacerbated when HDP was diagnosed, typically accompanied by increased peripheral vascular resistance compared to normotensive twins.

What are the clinical implications of this work?

The similarity in cardiac findings between singletons with HDP and normotensive twins, demonstrates the burden that a twin pregnancy places on the maternal cardiovascular system, which is further augmented in the presence of HDP. These findings should be considered when designing effective preventative strategies in these high-risk pregnancies.

ABSTRACT

Objectives: Twin pregnancies are at increased risk of developing hypertensive disorders of pregnancy (HDP) compared to singletons resulting in a substantially higher rate of maternal and perinatal complications. Despite this, the strain caused by a twin pregnancy on the maternal cardiovascular system is still poorly studied. The objective of this study was to evaluate the changes in maternal cardiac morphology and diastolic function in a cohort of women carrying normotensive and hypertensive twin pregnancies.

Methods: This was a cross-sectional study conducted at a tertiary referral university centre. Women with singleton or twin pregnancies were enrolled prospectively to undergo maternal transthoracic echocardiography throughout pregnancy. Multiple of median (MoM) were calculated for measured indices using a reference group of uncomplicated singleton pregnancies (n=411) in order to adjust for changes with gestational age. Cardiac findings were indexed to body surface area and compared among normotensive twins, singleton pregnancies complicated by HDP and twin pregnancies complicated by HDP.

Results: 119 HDP singletons, 52 normotensive twins and 24 HDP twins were included in the analysis. Left ventricle mass index (LVMi) MoM did not differ between singletons complicated by HDP and normotensive twins, but LVMi was significantly higher in HDP twins [1.31 (1.08-1.53) vs 1.17 (0.98-1.35), p=0.032]. Left atrial volume index MoM [1.12 (0.66-1.38) vs 0.65 (0.55-0.84), p=0.003] and diastolic index such as E/e' MoM [1.29 (1.09-1.54) vs 0.99 (0.99-1.02), p=0.036] were significantly higher in HDP twins when compared to normotensive twins. In normotensive twins compared to HDP singletons, stroke volume index (SVi) MoM was higher [1.20 (1.03-1.36) vs 1.00 (0.81-1.15), p=0.004] and total vascular resistance index (TVRi) was lower [0.73 (0.70-0.86) vs 1.29 (1.04-1.56), p<0.0001]. In contrast, SVi MoM was lower [1.10 (1.02-1.35) vs 1.20 (1.03-1.36), p=0.018] and TVRi was higher [1.00 (0.88-1.31) vs 0.73 (0.70-0.86), p=0.029] in hypertensive twins compared to normotensive twin pregnancies.

Conclusions: The maternal cardiovascular system is severely altered by a twin pregnancy with and without HPD. Despite a low total vascular resistance, cardiac changes in normotensive twins are comparable with those seen in singletons complicated by HDP reflecting the high cardiovascular demand imposed by a twin pregnancy.

KEYWORDS: pregnancy, twin pregnancy, echocardiography, preeclampsia, gestational hypertension, hypertensive disorders of pregnancy, cardiovascular, hypertension

INTRODUCTION

There has been a substantial increase in the twin pregnancy rate in Europe, North America, Asia and Africa from 1980 to date.[1] This rise has led to a significant clinical impact since twin pregnancies are associated with higher perinatal morbidity and morbidity, mainly due to prematurity, and maternal complications during pregnancy and delivery compared to singletons.[2,3] In particular, hypertensive disorders of pregnancy (HDP), including pre-eclampsia and gestational hypertension, are more frequent in twin compared to singleton pregnancy.[4, 5] This risk might be significantly underestimated because of the lower gestational age at delivery of multiple pregnancies compared to singleton. This leads to truncation of the data because most multiple gestations deliver before they can develop pre-eclampsia – with best estimates suggesting that pre-eclampsia is 8-10 times more common in twin compared to singleton pregnancy.[6]

Despite the clinical burden of twinning on maternal morbidity, research on pre-eclampsia and twin pregnancy is lacking. Several studies on maternal echocardiography have provided us with important information regarding the considerable impact of pregnancy-related changes on the maternal cardiovascular system in uncomplicated and hypertensive singleton pregnancies.[7-9] Conversely, only few studies have been published on the effect of twinning on maternal cardiovascular adaptation to pregnancy.[10-15] In uncomplicated twin pregnancies, maternal cardiac function and hemodynamic changes seemed to be more profound compared to uncomplicated singletons, presumably in order to supply the higher utero-placental demand. However, no study has compared maternal cardiac changes in multiple pregnancies to singletons with HDP.[11, 13-15]

The aim of the current study is to compare maternal echocardiographic changes among singleton complicated with HDP and twin pregnancies with and without HDP in a large cohort of women who underwent maternal echocardiography during pregnancy.

METHODS

This was a prospective cross-sectional study performed at St George's Hospital, University of London between 2008 and 2013. The local institutional review committee approved the study (Wandsworth Local Research Ethics Committee reference number: 01.78.5), and all participants provided written informed consent. Women with a viable singleton or twin pregnancy without genetic syndromes or major fetal abnormalities were recruited consecutively from the routine antenatal clinic, obstetric assessment unit, and antenatal ward throughout gestation. Pregnancy outcomes were ascertained from the maternity database and those cases with missing outcome information were excluded. Moreover, patients affected by pre-existing chronic hypertension or with any known cardiac condition were also not included in the analysis (Figure 1). Study diagnosis was confirmed by reviewing clinical records at delivery and the cohort was classified in three groups: 1) normotensive twin; 2) singleton complicated by HDP and 3) twin complicated by HDP. Singleton pregnancies without hypertension were recruited in the same period and setting and they were used as reference group.[8] HDP that included gestational hypertension and pre-eclampsia were defined by the International Society for the Study of Hypertension in Pregnancy (ISSHP) guideline.[16]

The study assessment included a medical and family history, measurement of anthropometric indices, blood pressure profile, conventional transthoracic echocardiography (TTE). Gestational age was determined by crown-rump length (CRL) or head circumference (HC) assessed by ultrasound, according to NICE guidelines.[17] The chorionicity was determined based on the presence or absence of the lambda sign at the intertwin membrane–placenta junction, as well as the intertwin membrane thickness at the site of its insertion in the chorion at 11-14 weeks.[18] Birthweight centile was calculated using birthweight standards by Poon et al.[19] Body mass index (BMI (kg/m^2)) was calculated by

dividing body weight (kg) by the squared height (m). Body surface area (BSA (m^2)) was measured using the following equation: 0.007184*height(cm)0.725*weight(kg)0.425. Systolic (SBP) and diastolic blood pressure (DBP) was obtained manually from the brachial artery using a mercury sphygmomanometer with the woman in a resting state using an appropriately sized cuff.[20] Mean arterial pressure (MAP) was calculated as (2*DBP+SBP)/3. TTE was performed at rest with patient in the left lateral decubitus position and data were acquired from standard parasternal and apical views using a GE Vivid E9 scanner (GE Healthcare, Horten, Norway).

Detailed methodology, repeatability and reproducibility of conventional echocardiographic indices were described in previous publications.[8, 21] Using the two-dimensional parasternal long-axis view, thickness of the interventricular septum (IVST, in mm), left ventricular end-diastolic diameter (LVEDd in mm) and the posterior wall thickness (PWT, in mm) were measured. Left ventricular mass (LVM (g)) was calculated using the formula 0.8*(1.04*(LVEDd+PWT+IVST)3−LVEDd3)+0.6 and indexed to BSA to obtain LVM index (LVMi). Relative wall thickness (RWT) was calculated as follows: RWT=2xPWd/LVEDd.[22] The following diastolic indices were measured: i) peak E-wave velocity (m/s) and the ratio of peak E-wave and peak A-wave velocity (E/A); ii) E/e′ where e′ is the average of septal e′ and lateral e′ obtained by pulsed-wave tissue doppler imaging (TDI) at the lateral and septal mitral annulus; iii) left atrial maximum volume indexed for BSA (LAVi (mL)). Stroke volume (SV) was calculated measuring the left ventricular outflow tract (LVOT) diameter, which was measured 3 to 10mm from the aortic valve plane in mid-systole with inner edge–to–inner edge methodology and the pulsed Doppler velocity time integral (VTI) in the 5-chamber view.[23] Heart rate (HR) was derived from electrocardiographic (ECG) monitoring. Total vascular resistance (TVR) was calculated using MAP×80/CO. SV and SVR were normalized for BSA to obtain SVi and TVRi.

Statistical Analysis

The analysis was performed using the statistical software package SPSS 27.0 (SPSS Inc., Chicago, IL, USA). Variables were assessed for normality by the Shapiro-Wilk test and by visualizing their histograms. Categorical data were presented as number (%) and compared using chi-square test of homogeneity or Fisher's exact test, as appropriate. Continuous variables were expressed as median and interquartile range (IQR). They were compared using Mann–Whitney U test, when the comparison involved two groups, and using Kruskal-Wallis test, when more than two groups were considered. In the latter case, post hoc tests such as Dunn's (1964) procedure with a Bonferroni adjustment were used to ascertain where any differences lied. Cardiac parameters were variable during gestation and, in order to adjust them for gestational age, multiple of the median (MoM) values were calculated for each cardiovascular index. Supplementary Table 1 showed baseline characteristics of the refence group of 411 singleton uncomplicated pregnancies. After checking for assumptions for linear regression equations, this population was used to calculate coefficients that were necessary to calculate the predictive values and, then, MoM value for each cardiac index. Linear regression models calculated using the reference group from 20 weeks were displayed by Supplementary Table 2. In the main analysis, only pregnancies assessed by TTE from 20 weeks' gestation were analyzed because cardiovascular changes begin early in pregnancy, reach their peak during the second and early third trimester, and then remain relatively constant until delivery,[24] while Supplementary Table 3 showed the analysis from the first to the third trimester. A value of $P<0.05$ was considered statistically significant.

RESULTS

Population description

The total cohort included 119 HDP singletons, 52 normotensive twins and 24 HDP twins who underwent TTE in the three trimesters (Table 1). In terms of chorionicity, 55 (72.4%) pregnancies were dichorionic and 21 (27.6%) were monochorionic diamniotic. The proportions of white ethnicity, maternal age and booking BMI were significantly different among groups. Gestational age at delivery showed significantly different medians among groups and this difference remained significant in pairwise comparison between HDP singletons and HDP twins (adjusted p=0.002) and between HDP singletons and normotensive twins (adjusted p=0.002).

Left ventricle geometry

There was no difference in RWT MoM among the three groups and LVMi MoM in normotensive twins did not differ from singletons complicated by HDP, but LVMi was significantly higher in HDP twins [1.31 (1.08-1.53) vs 1.17 (0.98-1.35), p=0.032] (Table 2). Figure 2 presents absolute values of LVMi in the three groups at different gestational age. Left chamber dimensions (LAVi, ESVi, EDVi) was significantly different between HDP singleton and normotensive twins (Table 2). LAVi MoM of HDP twins was higher than their normotensive counterparts [1.12 (0.66-1.38) vs 0.65 (0.55-0.84), p=0.003] (Figure 3) whilst ESVi MoM and EDVi MoM in HDP twin pregnancies were significantly higher when compared to HDP singletons, but not to normotensive twins (Supplementary Figure 1 and Figure 2).

Left ventricle function

Distribution of absolute values of E/A in the three groups are displayed in Figure 4. Peak E MoM, E/A MoM and E/e' MoM did not differ between normotensive twins and HDP singleton pregnancies (Table 2). While peak E MoM and E/A MoM did not change, E/e' MoM was significantly higher in HDP twins when compared to normotensive twins [1.29 (1.09-1.54) vs 0.99 (0.99-1.02), p=0.036].

Hemodynamic changes

SVi MoM was higher in normotensive twins compared to HDP singletons [1.20 (1.03-1.36) vs 1.00 (0.88-1.11), p=0.004], whereas it was lower in HDP twins compared with normotensive twins [1.10 (1.02-1.35) vs 1.20 (1.03-1.36), p=0.018]. TVRi MoM was lower in normotensive and HDP twins compared to HDP singletons, but higher in HDP twins compared to normotensive twins (Table 2, Figure 3).

DISCUSSION

Twin pregnancies are known to be affected by increased cardiovascular strain compared to singleton pregnancy. The findings of this study demonstrate that apart from lower TVRI, twin pregnancies exhibit geometric and functional cardiovascular indices equivalent to that seen in singleton pregnancies affected by HDP. Twin pregnancies affected by HDP showed higher values of LAVi MoM, E/e' MoM and TVRi MoM and lower SVi MoM compared to normotensive counterparts indicating more severe impairment of maternal cardiovascular function than that seen in normotensive twins or singleton HDP.

Interpretation of study findings and comparison with published literature

Most echocardiographic studies have investigated the comparison between uncomplicated twin pregnancies and singleton ones.[10, 11, 13-15, 25] Consistent with our results, LVM and SV was higher and increased at each gestation period in the former group compared to the latter, whereas peripheral vascular indices, such as TVR, were lower in twins than in singletons. In a longitudinal study including 30 uncomplicated twins a significant progressive worsening of left ventricle systolic and diastolic function (reduction of E-wave velocity, increase of A-wave and reduction of lateral and septal e') was observed from the first to the third trimester; however, conflicting results have been reported in other similarly studies.[10, 15, 25, 26] When twin pregnancies that developed HDP or small-for-gestational-age babies were compared to uncomplicated twin pregnancies, the only significant cardiovascular change was that TVR was higher in pathological pregnancies. The findings of the present study demonstrate that maternal cardiovascular function in normotensive twin pregnancies did not differ significantly from that in singleton pregnancies complicated by HDP. The latter illustrates the magnitude of the strain imposed by a twin pregnancy on the maternal cardiovascular system. Furthermore, when blood pressure and TVRi increased in twin pregnancies affected by HDP, a significant higher LVMi was detected by TTE compared to

hypertensive singleton pregnancy and a worsening of diastolic function occurred when compared with normotensive twins. These cardiovascular modifications might explain the lower SVi in HDP twins compared to normal twins.

Clinical Implications

The substantial maternal cardiovascular changes induced by twinning and, then, by hypertension, could explain the etiology and the increased incidence of HDP in multiple pregnancy. Pre-eclampsia in twin pregnancies might not result only from a primary underlying maternal cardiovascular phenotype, but mainly from the increased uteroplacental demand on the cardiovascular system that is not met, leading to placental hypoperfusion and the subsequent development of pre-eclampsia.[7] It is thought that the increased risk of pre-eclampsia in twin pregnancies may be due to enlarged placental mass that leads to increased circulating levels of soluble fms-like tyrosine kinase 1 (sFlt1).[27, 28] However, the excessive production of anti-angiogenetic factors might also be secondary to the above-mentioned placental hypoperfusion. Indeed, the cardiovascular hypothesis in twins affected by HDP is also supported by histopathological and epidemiological evidence. Firstly, histology of placentae from twin pregnancies complicated by pre-eclampsia, fetal growth disorders, or both, showed a lower prevalence of histological lesions related to placental insufficiency than those from their singleton counterparts – undermining a placental origins hypothesis for twin preeclampsia.[29-31] Secondly, a Swedish register-based study revealed that the risk of future cardiovascular diseases (CVD) in patients who had a multiple pregnancy with (adjusted HR 1.25, 95%CI 0.83-1.86) or without pre-eclampsia (adjusted HR 0.95, 95%CI 0.79-1.10) was not significantly increased as well as it was after a singleton pregnancy complicated by pre-eclampsia (adjusted HR 1.75, 95%CI 1.64-1.86).[32, 33] The latter finding suggests that the increased risk of CVD in singleton HDP is related to prenatal

maternal cardiovascular predisposition, but that in twins, excessive cardiovascular demand might be predominant and therefore not predispose to postnatal CVD.

The prediction model for the screening for pre-eclampsia in twins based on maternal factors, MAP, uterine artery pulsatility index (UtA-PI) and placental growth factor (PlGF) achieved a detection rate of 86.4%, with a 10% false-positive rate, for pre-eclampsia <32 weeks. Moreover, cardiovascular parameters, such as MAP, UtA-PI and PlGF, were more discriminative for pre-eclampsia in twins at earlier gestational ages compared to singleton pregnancies.[34] Although further and larger studies are necessary to prove that, it is expected that adding cardiac indices to this model might improve the ability to predict the development of pre-eclampsia in twin pregnancies.

Research Implications

It is undoubted that more studies on multiple pregnancies are warranted in order to reduce the rate of complications for mother and babies.[35] As demonstrated by the current study, maternal cardiovascular assessment can provide clinicians with important information. Currently, prescribing Aspirin 150 mg/day from the first trimester in multiple pregnancies is the only strategy recommended by several international guidelines to prevent pre-eclampsia.[36, 37] However, there is a low level of evidence supporting the use of Aspirin in twin pregnancies since the rate of resistance to aspirin 81 mg/day is reported to be as high as 65% and only mild forms of pre-eclampsia seemed to be prevented by prophylactic treatment.[38] The reason for the discrepancy in efficacy between singleton and twin pregnancies could be related to profound maternal cardiovascular changes as shown in the results of the current study. Further multi-centre studies based on maternal TTE should be designed to enhance the prevention and the management of these high-risk pregnancies at markedly increased risk of developing HDP.

Strengths and limitations

The main strengths of the study are ~~the large sample size,~~ the prospective design and the robust data derived from maternal TTE throughout pregnancy in the different groups of patients. Nevertheless, we acknowledge some limitations in the present study. Firstly, the cardiovascular assessment of our cohort was cross-sectional rather than longitudinal. Only a few cardiac indices to determine diastolic dysfunction was measured and therefore, compared. Likewise, more up-to-date techniques to assess LV systolic function, such as speckle tracking analysis, were not undertaken. A sub-analysis according to chorionicity was not undertaken because chorionicity does not seem to worsen maternal outcomes.[4] And, finally, pregnancies complicated by HDP and fetal growth restriction or inter-twin discrepancy were not analyzed separately since fetal growth trajectories are different between twins and singletons and, furthermore, it is still unknow how the maternal cardiovascular system in women affected by HDP might change with and without fetal growth restriction.[39, 40]

Conclusions

Uncomplicated twin pregnancies showed substantial maternal cardiovascular impairment during pregnancy similar to singleton pregnancies complicated by pre-eclampsia or gestational hypertension. Twin pregnancies complicated by HDP exhibit more severe changes in maternal cardiovascular function consistent with the severest presentations of preterm pre-eclampsia in singleton pregnancy. This information should be used to design future research on the topic to reduce the maternal morbidity and mortality related to cardiovascular complications in multiple pregnancy.

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CONFLICT OF INTEREST

The authors report no conflict of interest.

Table 1. Baseline characteristics of HDP singleton pregnancies, normotensive twin pregnancies and HDP twin pregnancies.

	Normotensive Twin N=52	**HDP Singleton N=119**	**HDP Twin N=24**	**P value**
Timing TTE				
< 15 weeks	21 (40.39)	10 (8.40)	3 (12.50)	
15-28 weeks	24 (46.15)	32 (26.89)	4 (16.67)	
> 28 weeks	7 (13.46)	77 (64.71)	17 (70.83)	
Maternal Age	34.00 (31-35)	32.00 (28-35)	32.50 (29-38.50)	0.045
Booking BMI (kg/m^2)	22.23 (20.43-25.43)	25.32 (22.37-29.98)	26.35 (22.20-28.70)	<0.0001
Ethnicity				
White	43 (82.69)	66 (55.46)	18 (75.00)	0.011
Black	3 (5.77)	27 (22.69)	2 (8.33)	
Asian	5 (9.62)	25 (21.01)	3 (12.50)	
Other	1 (1.92)	1 (0.84)	1 (4.17)	
Nulliparous	36 (69.23)	79 (66.39)	18 (75)	0.698
Family history of PE	2 (3.8)	19 (16.1)	2 (8.3)	0.066
Smokers	3 (5.77)	7 (5.88)	0	0.477
GA at delivery (weeks)	37.00 (35.00-37.43)	37.93 (34.57-39.43)	35.86 (34.86-37.00)	<0.0001
Birthweight (g)	2470.00 (2180.00-2840.00)	2742.50 (1850.00-3370.00)	2318.00 (2044.00-2600.00)	0.068
Birthweight Centile	23.09 (9.13-51.42)	17.89 (3.06-64.19)	16.05 (5.99-50.06)	0.808

TTE trans-thoracic echocardiography, BMI body mass index, GA gestational age, PE pre-eclampsia.

Table 2. Cardiac parameters and hemodynamics in HDP singleton pregnancies, normotensive twin pregnancies and HDP twin pregnancies after 20 weeks' gestation.

	Normotensive Twin (MoM)	**HDP Singleton (MoM)**	**HDP Twin (MoM)**	**Normotensive Twin vs HDP Singleton (p-value)**	**HDP Twin vs HDP Singleton (p-value)**	**Normotensive Twin vs HDP Twin (p-value)**
Left ventricle geometry						
LVMi	1.15 (1.06-1.32)	1.17 (0.98-1.35)	1.31 (1.08-1.53)	0.728	**0.032**	0.109
RWT	1.23 (1.08-1.35)	1.18 (1.01-1.37)	1.21 (0.96-1.41)	0.667	0.854	0.832
LAVi	0.65 (0.55-0.84)	1.09 (0.93-1.28)	1.12 (0.66-1.38)	**<0.0001**	0.761	**0.003**
ESVi	1.28 (1.05-1.45)	0.97 (0.74-1.32)	1.37 (1.04-1.75)	**0.003**	**0.002**	0.441
EDVi	1.23 (1.07-1.35)	1.03 (0.87-1.24)	1.28 (1.00-1.50)	**0.002**	**0.003**	0.456
Left ventricle function						
E	1.04 (0.86-1.13)	1.00 (0.84-1.21)	1.08 (0.99-1.16)	0.896	0.158	0.204
E/A	0.94 (0.72-1.07)	0.86 (0.69-1.13)	0.95 (0.79-1.26)	0.886	0.203	0.204
E/e'	0.99 (0.99-1.02)	1.11 (0.97-1.46)	1.29 (1.09-1.54)	0.355	0.196	**0.036**
Hemodynamic changes						
HR	1.02 (0.93-1.13)	1.00 (0.88-1.11)	0.98 (0.79-1.13)	0.389	0.274	0.535
SVi	1.20 (1.03-1.36)	1.00 (0.81-1.15)	1.10 (1.02-1.35)	**0.004**	0.733	**0.018**
TVRi	0.73 (0.70-0.86)	1.29 (1.04-1.56)	1.00 (0.88-1.31)	**<0.0001**	**<0.0001**	**0.029**

MoM Multiple of median, HDP hypertensive disorders of pregnancy, LVMi left ventricle mass index, RWT relative wall thickness, LAVi left atrium volume index, ESVi end-systolic volume index, EDVi end-diastolic volume index, HR heart rate, SVi stroke volume index, TVRi total vascular resistance index. Data are expressed as Median (IQR)

Figure legends

Figure 1. Population selection process.

Figure 2. Left ventricle mass index. Scatter plot of left ventricle mass (LVM) index in HDP singletons, normotensive twins and HDP twins and linear regression (continuous line) between E/A and gestational age with 95% confidence intervals (dotted lines) in normotensive singletons (reference group).

Figure 3. Left atrium volume index MoM and total vascular resistance index MoM. Box plots for left atrium volume index (LAVi) MoM and total vascular resistance index (TVRi) MoM in HDP singletons, normotensive twin and HDP twins after 20 weeks. MoM were calculated using normotensive singleton pregnancies as reference (dotted line at MoM=1).

Figure 4. Mitral E/A ratio using pulsed Doppler. Scatter plot of E/A in HDP singletons, normotensive twins and HDP twins and linear regression (continuous line) between E/A and gestational age with 95% confidence intervals (dotted lines) in normotensive singleton (reference group).