Maternal cardiac function in gestational diabetes mellitus at 35–36 weeks' gestation and after six months postpartum

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Contribution

What are the novel findings of this work

At 35-36 weeks' gestation, women with GDM, compared to controls, have mild impairment in left ventricular systolic and diastolic indices and this impairment persists for at least six months after delivery.

What are the clinical implications of this work

In women who develop GDM further studies are needed to determine whether with increasing age and accumulation of cardiovascular risk factors, the cardiovascular changes observed during pregnancy and for at least six months after delivery are accentuated and contribute to the increased long-term cardiovascular risk of these women.

ABSTRACT

Background: Women with gestational diabetes mellitus (GDM) are at increased risk for adverse cardiovascular outcome later in life. However, it is uncertain whether this increased risk is due to cardiovascular changes occurring during pregnancy and persisting thereafter or to an adverse underlying cardiovascular risk factor profile. Few studies have reported that GDM is associated with reduced systolic and diastolic left ventricular function in pregnancy however it remains unknown whether these changes persist after delivery. The objective of this study is to compare maternal cardiac function and structure in women with GDM and those with uncomplicated pregnancy at 35-36 weeks' gestation and about six months after delivery.

Methods: This is a longitudinal study where women with GDM and those with uncomplicated pregnancy had detailed cardiovascular assessment at 35-36 weeks' gestation and repeat examination around six months after delivery. In all women, left ventricular systolic and diastolic indices were measured and left ventricular mass indexed for body surface area was calculated. Cardiac output and peripheral vascular resistance were also calculated using echocardiography. Linear mixed model analysis accounting for differences in maternal characteristics was carried out to compare findings in cardiovascular function between the GDM group and controls and within each group at 35-36 weeks' gestation and at six months after delivery.

Results: We studied 73 women with GDM and 73 controls with uncomplicated pregnancies. At 35-36 weeks' gestation, women with GDM, compared to controls, had higher E/e' ratio and lower E/A ratio and global longitudinal systolic function; there were no significant differences between the groups in ejection fraction and myocardial performance index. Left ventricular mass indexed for body surface area was also increased in GDM women. There were no significant differences between the groups in cardiac output and peripheral vascular resistance. At one year after delivery, cardiac functional indices improved for both the GDM patients and controls, but in the GDM group, compared to controls, there was a lower degree of improvement in E/A ratio and global longitudinal systolic function.

Conclusion: In the third trimester, GDM patients have subtle differences in diastolic and systolic left ventricular function compared to controls and despite improvement after delivery, these changes persist for at least six months. Long term follow up therefore is needed to assess whether GDM women are at risk for an accelerated decline in their cardiac function and if so whether this trend can be reversed or delayed by optimal cardiovascular risk factor modification.

INTRODUCTION

The incidence of gestational diabetes mellitus (GDM) is increasing because of increasing maternal age and obesity and reduced physical activity[1]. Although, by definition, the glucose intolerance is transient, GDM is associated with both short-term and long-term adverse health outcomes for both the mother and fetus / child[2]. Women with GDM have up to 70% risk of progressing to type 2 diabetes in the first decade after delivery[3] and an increased risk for later cardiovascular disease, which is not necessarily mediated by development of diabetes[4-7]. However, it is difficult to decipher whether the transient exposure to hyperglycemia during pregnancy is the stimulus for acute cardiovascular changes which persist after delivery and increase the long term cardiovascular risk for these women or whether GDM is an early subclinical expression of metabolic syndrome and the later cardiovascular risk relates not to acute cardiac changes but to an untreated abnormal cardiovascular risk factor profile.

Previously, we have demonstrated that women with GDM at 35-36 weeks' gestation, compared to controls, have evidence of subclinical left ventricular dysfunction with higher diastolic and lower systolic functional indices[8], but it remains unclear whether these functional changes persist in the postpartum period. The objective of this study is to compare maternal cardiac function and structure in women with GDM and those with uncomplicated pregnancy at 35-36 weeks' gestation and at about six months after delivery and assess whether the rate of cardiovascular recovery differs between women with GDM and controls.

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METHODS

Study design and participants

Our study population included women who attended the Harris Birthright Unit for a routine ultrasound scan at 35-36 weeks' gestation for assessment of fetal growth and wellbeing and participated in the Advanced Cardiovascular Imaging Study (REC No 18/NI/0013, IRAS ID:237936). In the current substudy, we have invited women with singleton pregnancies who were diagnosed with GDM and an equal number of control women who had uncomplicated pregnancies and were assessed contemporaneously with the GDM participants for a repeat cardiovascular assessment at about 6 months after delivery. We excluded women with prior known cardiovascular disease, gestational or pre-existing hypertensive disorder, fetal structural defects or chromosomal abnormalities. Women with breast implants were also excluded as these commonly compromise the echocardiographic acoustic windows[9]. All women provided written informed consent to participate in the study.

Maternal characteristics

We recorded information on maternal age, racial origin (White, Black, Asian and mixed), method of conception (natural or assisted by *in-vitro* fertilization or use of ovulation drugs), cigarette smoking during pregnancy, medical history, parity (parous and nulliparous if there was no previous pregnancy with delivery at ≥24 weeks´ gestation). Weight and height were measured at the first hospital visit at 11-13 weeks' gestation; 3the wait was also measured at the visit for assessment at 35-36 weeks and postpartum. Body mass index was calculated. Diagnosis of GDM was made by performing the two- step approach recommended by NICE guidelines[10].

Maternal cardiovascular assessment

Mean arterial pressure was measured, both at the 35-36 weeks' gestation visit and at the postpartum visit, using validated devices and a standardized protocol[11]. Maternal echocardiography was performed using a Canon Aplio i900 scanner (Canon Medical Systems Europe BV, ZOETERMEER, The Netherlands). The protocol included standard parasternal and apical views as per American Society of Echocardiography (EAE/ASE) guidelines[12]. In all women we measured hemodynamic parameters, including cardiac output and peripheral vascular resistance, and detailed systolic and diastolic left ventricular assessment as previously described. Left atrial area was calculated in end-systole from the four-chamber view. Left ventricular mass was calculated with the Devereux formula using measurements of the anatomical M-mode applied in the parasternal long axis. The mitral peak early (E) and late (A) diastolic flow velocities were measured, and the E/A ratio was calculated. Pulsed tissue Doppler recordings were obtained at the septal and lateral aspects of basal left ventricle at the junction with the mitral valve annulus in the apical four-chamber view. The E/e' ratio was calculated using the mean value between septal and lateral peak

e' waves. Speckle tracking was employed to assess global longitudinal function of the left ventricle (Figure 1).

Pregnancy outcomes

Data on pregnancy outcome were collected from hospital delivery records or the general medical practitioners. Birth weight for gestational age was converted to a Z-score based on the Fetal Medicine Foundation fetal and neonatal weight chart[13].

Statistical analysis

Normally distributed continuous variables are presented as mean (± standard deviation) and variables not following normal distribution as median (25^{th} - 75^{th} percentile). Nominal variables are summarized as counts and absolute percentages. Distribution of continuous variables was graphically assessed by histograms and quantile-quantile plots. Maternal cardiac measurements were compared between GDM and controls with the independent samples Student's T Test or the Mann-Whitney U Test and the chi-squared test for continuous and categorical variables, respectively. General linear regression models were used to assess the association between GDM and a range of echocardiographic parameters. In terms of power calculation for this study, we estimated that a sample size of 71 women per group would provide adequate power (85%) to detect a minimum increase of 0.7 units in E/e' between GDM and controls, assuming an interquartile range of 2 units in both groups. The effect size and the measures of dispersion were derived from previously published data from our group in a comparable study of women with GDM and uncomplicated pregnancies[8]. The power analysis was based on the non-parametric Mann Whitney test and conducted with G* Power 3.1.9.4

To facilitate the comparison of changes in echocardiographic parameters before and after pregnancy for the two groups of interest, we used linear mixed models with two random effects (random intercept and random slope) and an unstructured variance-covariance matrix. Maternal cardiac parameters which were used as outcome variables included structural markers (left ventricular mass indexed for body surface area) and functional parameters (E/A, E/E', GLS, myocardial performance index) which were previously shown to be altered during pregnancy as part of the maternal cardiovascular adaptation[8]. An interaction term [GDM yes/no*visit (pre-versus postpartum] was introduced in linear mixed models to evaluate the potential differential effect of GDM on changes in cardiac measurements before and after delivery. Analysis was further adjusted for a pre-specified set of confounders, including maternal age, race, parity, weight, height, mean arterial pressure, heart rate and time elapsed from delivery to second visit. To ensure normality of distribution of dependent variables in linear mixed models, the analysis was repeated after inverse ranking normalisation of maternal cardiac markers[14].

Statistical analysis was conducted with STATA package, version 13.1 (StataCorp, College Station, Texas USA). We deemed statistical significance at $p < 0.05$. All tests were 2-tailed.

RESULTS

Study population

The characteristics of the study population of 73 women with GDM and 73 women with uncomplicated pregnancies are shown in Table 1. In the GDM group, compared to controls, the maternal age and incidence of Black and South Asian racial origin were higher, and median gestational age at delivery and birthweight were lower. GDM women had reduced weight gain during pregnancy compared to controls, 23 women were treated by diet alone, 24 by metformin, 10 by insulin and 16 by a combination of metformin and insulin. At the visit one year after delivery, GDM women had higher weight compared to controls.

Cardiovascular assessment at 35-36 weeks' gestation

Women with GDM, compared to controls, had higher E/e' ratio and lower E/A ratio and global longitudinal systolic function; there were no significant differences between the groups in ejection fraction and myocardial performance index (Table 2). Left ventricular mass indexed for body surface area was also increased in GDM women (Table 2), but there was no significant difference between the groups after multivariable analysis (Table 3). There were no significant differences between the groups in cardiac output and peripheral vascular resistance (Table 2). Subgroup analysis in women with GDM demonstrated no significant differences in cardiovascular indices according to diabetic treatment (Supplementary Table 1).

Cardiovascular assessment six months after delivery

At around six months after delivery, there was improvement in systolic and diastolic cardiac indices in both the GDM patients and the controls (Table 2; Figure 2). From the left ventricular diastolic indices, E/A was lower whereas E/e' was similar between GDM and controls. There was no significant difference in left atrial volume and left ventricular mass indexed for body surface area between the groups. From the left ventricular systolic functional indices, global longitudinal systolic function remained lower in women with GDM compared to controls. There were no significant differences between the groups in cardiac output and peripheral vascular resistance. Diabetic treatment did not modify the cardiac indices at around six months after delivery (Supplementary Table 2).

In the assessment of change in cardiovascular indices between the prenatal and postnatal assessment, in women with GDM, compared to controls, there was a lower degree of improvement in E/A and in global longitudinal systolic function (Table 3, Figure 1). In women with GDM, the rate of improvement in E/e' was greater in women who received metformin or insulin during pregnancy compared to controls (Supplementary Table 3).

DISCUSSION

Main findings

In the current study, we performed detailed cardiovascular assessment in women with GDM and controls at 35-36 week's gestation and we followed up these women for around six months after delivery. This evaluation allowed us to explore differences in cardiovascular adaptations in pregnancy between women with GDM and controls but also enabled us to detect persistent cardiovascular alterations outside the peripartum period. Consistent with our previous results[8], women with GDM, compared to women with uncomplicated pregnancy, had reduced left ventricular diastolic function and lower left ventricular systolic functional indices at 35-36 weeks' gestation. Left ventricular mass was also increased. Although, left ventricular remodeling with reduction in systolic and diastolic cardiac indices is considered to be a physiological response to increase in volume loading in pregnancy[15,16], our data suggest that women with GDM despite optimal management demonstrate accentuated response to cardiovascular adaptation in pregnancy. At six months after delivery cardiac indices improved in both the women with GDM and controls but in the GDM group there was a lower degree of improvement in left ventricular myocardial relaxation and in global longitudinal systolic function.

Considering that the reported left ventricular functional changes are subtle, and reported values are well within the normal range for non-pregnant adults[17], further studies are needed to determine whether with increasing age and accumulation of cardiovascular risk factors, these cardiovascular changes are accentuated and contribute to the increased long-term cardiovascular risk of women that develop GDM.

Interpretation of results and comparison with previous studies

Previous studies have shown that although the hyperglycemic phenotype in women with GDM resolves with delivery, these women continue to be at increased risk for adverse health outcomes[18]. For instance, history of GDM has been associated with increased cardiovascular risk later in life; although this association was initially attributed to development of type 2 diabetes[18-20], a number of cohort studies and a recent meta-analysis suggest that this link exists even in the absence of type 2 diabetes [18-22]. However, it is uncertain whether the reported association between GDM and cardiovascular risk is the result of the hyperglycemic insult on the cardiovascular system during pregnancy or due to prolonged exposure to an adverse cardiovascular risk factor profile, before, during and after pregnancy. Insulin resistance, obesity and elevated inflammatory markers have been reported in women that developed GDM several years after the index pregnancy and these may increase their cardiovascular risk[23-25]. In the current study, women with GDM were older, and were more of Black racial origin. Weight at first visit and at six months after delivery was higher in women with GDM compared to controls whereas weight gain and birthweight were lower consistent with the optimal management of GDM during pregnancy. However, despite optimal glucose management and following

adjustment for changes in cardiovascular risk factor profile, we showed that GDM is associated with functional alteration on the maternal cardiovascular system during pregnancy and persistence of left ventricular functional changes for at least one year after delivery.

For healthy women, cardiovascular functional parameters return to pre-pregnancy levels few months after delivery. However, in women with GDM cardiovascular functional changes may persist long after delivery and may contribute to their reported increased long-term cardiovascular risk. Consistent with this, is our finding that cardiac functional indices improved in both the GDM and control groups after delivery. However, indices of left ventricular relaxation and longitudinal shortening function remained lower in women with GDM compared to controls. Our results complement data from a small study of 13 women with GDM and 13 controls where mild deterioration in left ventricular diastolic indices was noted 8 weeks postpartum in women with GDM[26]. In our study, mitral valve A wave Doppler contraction was higher in women with GDM and E/A ratio was reduced both at 35-36 week's gestation and at six months after delivery. Change in A velocity is often age related and reflects slowing of myocardial relaxation which predisposes older individuals to the development of diastolic heart failure. In the current study, women with GDM were older and had higher heart rate compared to controls. However, differences in E/A between groups persisted after accounting for differences in maternal characteristics. Tissue Doppler indices were comparable between women with GDM and controls after delivery.

From left ventricular systolic functional parameters, peak global longitudinal strain remained lower in women with GDM at six months after delivery, whereas ejection fraction and myocardial performance index were comparable between groups. These findings are in agreement with the knowledge that changes in myocardial deformation are the first detectable preclinical functional alterations and would be consistent with the physiology noted in heart failure patients where ejection fraction is preserved in the presence of mild diastolic functional deterioration as noted in our population.

History of GDM has also been associated with changes in left ventricular mass. In the CARDIAC study[27], 64 women with GDM and 545 with uncomplicated pregnancy were followed up with echocardiography 5 and 25 years after delivery. At 5 years, no significant differences in echocardiographic parameters were noted between women with GDM and controls with uncomplicated pregnancy, whereas at 25 years, women with history of GDM had increased left ventricular mass. Left ventricular mass index was increased in GDM women during pregnancy but this difference normalized in the postpartum assessment and this is consistent with the findings of the CARDIAC study at first evaluation at 5 years. Our results also suggest that structural left ventricular changes reported in women with GDM later in life are unlikely to be associated with the acute glycemic insult during pregnancy.

Strengths and limitations

This is the first study to perform detailed cardiovascular assessment on GDM and healthy women at 35-36 weeks' gestation with repeat echocardiography at six months after delivery. Women with GDM were carefully monitored during pregnancy to achieve optimal glucose control and fellows who were trained in echocardiography performed all cardiac measurements. Postpartum cardiovascular assessment was planned for few months after delivery to minimize the confounding effect of acute hemodynamic changes noted in the peripartum period. After delivery women with GDM were assessed around three months earlier than the controls and although we accounted for this time difference in our analysis, we cannot exclude that this may also contribute for the subtle differences between groups. Another limitation of the study is that we did not have cardiovascular information before pregnancy or prior to development of GDM and it therefore remains unknown whether GDM unmasks a women's pre-existing cardiovascular subclinical abnormality or is actually a mediator of future cardiovascular pathogenesis.

Conclusions

In conclusion, our study demonstrates that despite optimal glucose management during pregnancy, GDM patients have subtle differences in diastolic and systolic left ventricular function compared to controls and despite improvement after delivery, these changes persist to at least six months after delivery. Long term follow up therefore is needed to assess whether women with GDM are at risk for an accelerated decline in their cardiac function and if so whether this trend can be reversed or delayed by optimal cardiovascular risk factor modification.

Conflict of interest: The authors report no conflict of interest

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REFERENCES

1. Association AD. Classification and diagnosis of diabetes: standards of medical care in diabetes—2019. *Diabetes Care* 2019; **42**: S13-S28.

2. Malcolm J. Through the looking glass: gestational diabetes as a predictor of maternal and offspring long-term health. *Diabetes Metab Res Rev* 2012; **28**: 307-311.

3. Bellamy L, Casas J-P, Hingorani AD, Williams D. Type 2 diabetes mellitus after gestational diabetes: a systematic review and meta-analysis. *The Lancet* 2009; **373**: 1773-1779.

4. Retnakaran R. Hyperglycemia in pregnancy and its implications for a woman's future risk of cardiovascular disease. *Diabetes Res Clin Pract* 2018;**145**:193-199.

5. Tobias DK, Stuart JJ, Li S, Chavarro J, Rimm EB, Rich-Edwards J, Hu FB, Manson JE, Zhang C. Association of history of gestational diabetes with long-term cardiovascular disease risk in a large prospective cohort of US women. *JAMA Intern Med* 2017; **177**: 1735-1742.

6. Goueslard K, Cottenet J, Mariet A-S, Giroud M, Cottin Y, Petit J-M, Quantin C. Early cardiovascular events in women with a history of gestational diabetes mellitus. *Cardiovasc Diabetol* 2016; **15**:15.

7. Kramer CK, Campbell S, Retnakaran R. Gestational diabetes and the risk of cardiovascular disease in women: a systematic review and meta-analysis. *Diabetologia* 2019; **62**: 905-914.

8. Aguilera J, Semmler J, Coronel C, Georgiopoulos G, Simpson J, Nicolaides KH, Charakida M. Paired maternal and fetal cardiac functional measurements in women with gestational diabetes mellitus at 35-36 weeks' gestation. *Am J Obstet Gynecol* 2020 doi:10.1016/j.ajog.2020.04.019.

9. Movahed M-R. Impairment of echocardiographic acoustic window caused by breast implants. *Eur J Echocardiogr* 2008; **9**: 296-297.

10. Walker J. NICE guidance on diabetes in pregnancy: management of diabetes and its complications from preconception to the postnatal period. NICE clinical guideline 63. London, March 2008. Diabet Med 2008; **25**: 1025-1027.

11. Poon L, Zymeri N, Zamprakou A, Syngelaki A, Nicolaides KH. Protocol for measurement of mean arterial pressure at 11-13 weeks' gestation. *Fetal Diagn Ther* 2012; **31**: 42-48.

12. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2015; **16**: 233-271.

13. Nicolaides KH, Wright D, Syngelaki A, Wright A, Akolekar R. Fetal Medicine Foundation fetal and neonatal population weight charts. *Ultrasound Obstet Gynecol* 2018; **52**: 44-51.

14. Stamatelopoulos K, Georgiopoulos GA, Athanasouli F, Nikolaou P-E, Lykka M, Roussou M, Gavriatopoulou M, Laina A, Trakada G, Charakida M. Reactive Vasodilation Predicts Mortality in Primary Systemic Light Chain (AL) Amyloidosis. *Circ Res* 2019; **125:** 744-758

15. 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**: 360-368.

16. Melchiorre K, Sharma R, Khalil A, Thilaganathan B. Maternal cardiovascular function in normal pregnancy: evidence of maladaptation to chronic volume overload. *Hypertension* 2016; **67**: 754-762.

17. Galderisi M, Cosyns B , Edvardsen T, Cardim N, Delgado V, Di Salvo G, Donal E, Elif Sade L, Ernande L, Garbi M, Grapsa J,Hagendorff A, Kamp O, Magne J, Santoro C, Stefanidis S, Lancellotti P, Popescu B, Habib G. Standardization of adult transthoracic echocardiography reporting in agreement with recent chamber quantification, diastolic function, and heart valve disease recommendations: an expert consensus document of the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2017; **18**: 1301-1310.

18. Shah BR, Retnakaran R, Booth GL. Increased risk of cardiovascular disease in young women following gestational diabetes mellitus. *Diabetes Care* 2008; **31**: 1668-1669.

19. Gunderson EP, Chiang V, Pletcher MJ, Jacobs Jr DR, Quesenberry Jr CP, Sidney S, Lewis CE. History of gestational diabetes mellitus and future risk of atherosclerosis in mid-life: the coronary artery risk development in young adults study. *J Am Heart Assoc* 2014; **3**: e000490.

20. Carr DB, Utzschneider KM, Hull RL, Tong J, Wallace TM, Kodama K, Shofer JB, Heckbert SR, Boyko EJ, Fujimoto WY. Gestational diabetes mellitus increases the risk of cardiovascular disease in women with a family history of type 2 diabetes. *Diabetes Care* 2006; **29**: 2078-2083.

21. McKenzie-Sampson S, Paradis G, Healy-Profitós J, St-Pierre F, Auger N. Gestational diabetes and risk of cardiovascular disease up to 25 years after pregnancy: a retrospective cohort study. *Acta Diabetol* 2018; **55**: 315-322.

22. Sullivan SD, Umans JG, Ratner R. Gestational diabetes: implications for cardiovascular health. *Curr Diab Rep* 2012; **12**: 43-52.

23. Di Benedetto A, Russo GT, Corrado F, Di Cesare E, Alessi E, Nicocia G, D'Anna R, Cucinotta D. Inflammatory markers in women with a recent history of gestational diabetes mellitus. *J Endocrinol Invest* 2005; **28**: 34-38.

24. Kousta E, Lawrence NJ, Godsland IF, Penny A, Anyaoku V, Millauer BA, Cela E, Johnston DG, Robisnon S, McCarthy MI. Insulin resistance and β-cell dysfunction in normoglycaemic European women with a history of gestational diabetes. *Clin Endocrinol (oxf)* 2003; **59**: 289-297.

25. Ilercil A, Devereux RB, Roman MJ, Paranicas M, O'Grady MJ, Welty TK, Robbins DC, Fabsitz RR, Howard BV, Lee ET. Relationship of impaired glucose tolerance to left ventricular structure and function: the Strong Heart Study. *Am Heart J* 2001; **141**: 992-998.

26. Freire CMV, Nunes MdCP, Barbosa MM, de Oliveira Longo JR, Nogueira AI, Diniz SSA, Machado LJC, de Oliveira Jr AR. Gestational diabetes: a condition of early diastolic abnormalities in young women. *J Am Soc Echocardiogr* 2006; **19**: 1251-1256.

27. Appiah D, Schreiner PJ, Gunderson EP, Konety SH, Jacobs DR, Nwabuo CC, Ebong IA, Whitham HK, Goff DC, Lima JA. Association of gestational diabetes mellitus with left ventricular structure and function: the CARDIA study. Diabetes Care 2016; **39**: 400-407.

Figure legends

Figure 1. Speckle tracking analysis in a woman with GDM (left) and one with uncomplicated pregnancy (right)
The software traces the myocardium of the left ventricle and myocardial deformation is shown in the graph. Global longitudinal peak systolic strain in the 4-chamber view is calculated. Similar measurements are performed in the 3-chamber and 2-chamber view and the average global longitudinal peak strain of the left ventricle is calculated. The endiastolic and endsystolic volume and ejection fraction are derived.

Figure 2. Cardiac indices in women with GDM and controls at 35-36 weeks' gestation and at six months postpartum. All cardiac indices improved after delivery however the rate of improvement was lower in GDM patients for E/A ratio and global longitudinal systolic function compared to controls. For E/e' ratio, a significant decrease was noted in women with GDM at six months after delivery whereas only marginal change in E/e' was noted in the controls.

Table 1. Characteristics of the study population

Variable	Controls (n=73)	GDM (n=73)	P-Value
Age in years	32.6(4.3)	35.1(5.5)	0.004
Racial origin			
White	58 (79.5)	36 (49.3)	0.002
Black	7 (9.6)	21 (28.8)	
Asian	6 (8.2)	13 (17.8)	
Mixed	2 (2.7)	3 (4.1)	
Parous	36 (49.3)	44 (60.3)	0.244
Conception by IVF	4 (5.5)	6 (8.2)	0.495
Smoking	1 (1.4)	2 (2.7)	0.500
Gestation at delivery in weeks	40.1 (39.3, 40.9)	39.3 (38.5, 40.1)	<0.001
Birthweight in g	3540 (3255, 3820)	3385 (3145, 3705)	0.047
Birthweight (z score)	0.1 (1.2)	0.1(0.9)	0.801
Height in cm	165.1(7.6)	164.6 (6.2)	0.674
Weight at 11-13 weeks' gestation in Kg	76.7 (15.8)	69.2 (12.6)	0.004
Assessment at 35-36 weeks' gestation			
Gestational age in weeks	36.1 (35.8, 36,4)	36.0 (35.7, 36.4)	0.065
Weight in Kg	80.9 (12.6)	84.7 (14.5)	0.101
Body mass index in Kg/cm^2	29.8(4.8)	31.2(5.1)	0.078
Mean arterial pressure in mmHg	87.2 (6.6)	88.9 (8.2)	0.172
Weight gain in Kg	11 (9.0,14.5)	8.8 (5.1,11.7)	<0.001
Glycosylated hemoglobin in %		5.6(0.5	
Postnatal assessment			
Interval from delivery in months	11.2 (3.0)	8.1 (3.8)	<0.001
Weight in Kg	69.2 (14.1	79.5 (16.1)	<0.001
Body mass index in Kg/cm^2	25.5 (5.2)	29.3 (5.8)	<0.001
Mean arterial pressure in mmHg	84.4 (7.4)	86.1 (11.3)	0.303

Values presented as mean (standard deviation) or median (interquartile range). P values are derived from the independent samples Student's t-test or the Mann-Whitney U test and the chi-squared test for continuous and categorical variables, respectively.
Abbreviations: GDM = Gestational diabetes mellitus

Table 2. Comparison of maternal cardiac parameters between women with GDM and controls at 35-36 weeks' gestation and one year postpartum

Variable	Assessment at 35-36 weeks' gestation			Assessment postpartum		
	Controls	GDM	P-Value	Controls	GDM	P-Value
Left ventricular diastolic indices						
E/A	1.4 (1.2,1.7)	1.3 (1.1, 1.5)	0.028	2.1 (1.5, 2.8)	1.5 (1.2, 1.8)	<0.001
Mitral peak early diastolic flow velocity (E) in cm/sec	77.1 (64.9,86.4)	75.2 (62.4, 87.7)	0.019	83.3 (68.9, 92.4)	75.4 (66.4, 84.2)	0.025
Mitral peak late diastolic flow velocity (A) in cm/sec	52.8 (45.9, 59.0)	55.5 (48.3, 72.2)	0.759	39.0 (31.6, 48.1)	50.6 (39.4, 65.3)	<0.001
E/e'	5.6 (4.6,6.8)	6.6 (4.9, 7.7)	0.006	5.8 (5.0, 6.5)	5.6 (5.1, 6.9)	0.399
Tissue Doppler early diastolic flow velocity (e') in cm/sec	13.5 (11.8, 15.1)	11.9 (10.5, 13.6)	0.002	14.1 (13.1, 15.3)	12.8 (11.0, 14.9)	0.001
Tissue Doppler late diastolic flow velocity (A') in cm/sec	8.0 (7.2, 9.4)	8.2 (7.1, 9.3)	0.626	7.6 (6.8, 8.6)	7.8 (6.9, 9.4)	0.242
Isovolumic contraction time in msec	57 (50, 68)	58 (49, 68)	0.893	67 (58,78)	69 (60,81)	0.647
Isovolumic relaxation time in msec	67 (56,83)	75 (58, 91)	0.062	61.0 (47.0, 69.0)	56 (47, 67)	0.062
Left atrial volume indexed for body surface area	18.6 (15.6, 22.0)	18.1 (14.9, 22.4)	0.348	19.9 (17.3, 23.9)	19.0 (16.1, 22.3)	0.086
Left atrial area in cm^2	13.8 (12.0, 15.3)	14.1 (11.7, 16.6)	0.683	14.3 (12.8, 16.4)	14.4 (12.4, 16.2)	0.779
Left ventricular systolic indices						
Myocardial performance index	0.5 (0.4, 0.6)	0.5 (0.5, 0.6)	0.025	0.4 (0.4, 0.5)	0.5 (0.4, 0.5)	0.051
Tissue Doppler systolic flow velocity (S) in cm/sec	10.2 (9.2, 11.6)	9.7 (8.6, 10.6)	0.006	9.7 (8.7, 10.5)	9.4 (8.6, 10.8)	0.639
Global longitudinal systolic function in %	-21.7 (-23.8, -19.8)	-20.7 (-22.2, -19.3)	0.018	-24.6 (-26.9, -22.6)	-22.3 (-24.3, -20.5)	<0.001
Global circumferential stain in %	-29.1 (-31.6, -25.9)	-27.8(-31.1,-24.6)	0.210	-30.2(-33.2,-27.5)	-31(-34.1,-26.4)	0.829
Ejection fraction in %	60.1 (53.3, 65.6)	59.2 (53.8, 63.4)	0.190	60.9 (54.2, 68.6)	59.2 (53.1, 64.8)	0.219
Hemodynamic parameters						
Peripheral vascular resistance in dynes/sec	1292 (1163,1545)	1395 (1151, 1705)	0.286	1323 (1217, 1524)	1344 (995, 1579)	0.336
Cardiac output in L/min	5.3 (4.7, 5.9)	5.0 (4.3, 5.9)	0.376	5.1 (4.4, 5.5)	5.1 (4.3, 6.0)	0.292
Left ventricular structure						
Left ventricular mass indexed for body surface area	57.1 (51.5, 63.4)	62.7 (55.6, 72.2)	0.003	61.1(54, 68.4)	59.0 (52.7, 65.8)	0.555

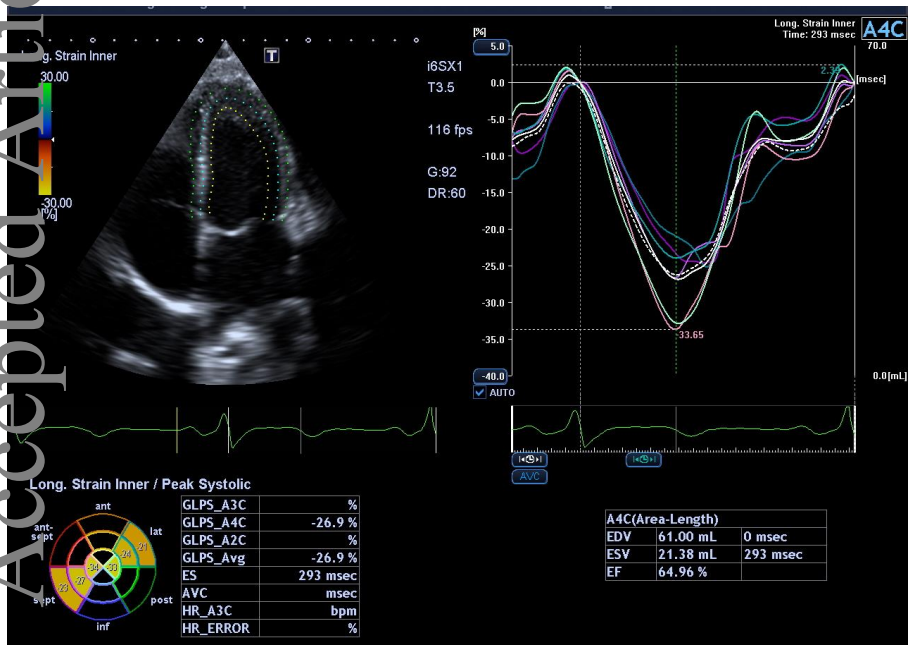
Values presented as median (interquartile range). P-values are derived from the non-parametric Mann-Whitney U test. diabetes mellitus

Abbreviations: GDM = Gestational diabetes mellitus

Table 3. Linear mixed model analysis of longitudinal changes in maternal cardiac indices according to GDM status

Variables	Differences in cardiac indices adjusted for age, height, race, parity, changes in weight, heart rate, mean arterial pressure and time to second visit									
	Between GDM and controls at 35-36 weeks' gestation (visit 1)		Between GDM and controls at 1 year post delivery (visit 2)		Controls visit 1 and visit 2		GDM visit 1 and visit 2		Interaction [group*time]	
	Mean difference (95%CI)	P-Value	Mean difference (95%CI)	P-Value	Mean difference (95%CI)	P-Value	Mean difference (95%CI)	P-Value	Coefficient (95%CI)	P-Value
Left ventricular diastolic indices										
E/A	-0.2 (-0.3, -0.05)	0.008	-0.6 (-0.9, -0.3)	<0.001	0.6 (0.4, 0.8)	<0.001	0.2 (-0.1, 0.4)	0.137	-0.4 (-0.7, -0.1)	0.005
Mitral peak early diastolic flow velocity (E), cm/sec	-0.5 (-5.5, 4.6)	0.861	-4.5 (-9.3, 0.3)	0.066	4.6 (0.2, 8.9)	0.041	0.5 (-3.7, 4.7)	0.818	-4.1 (-9.7, 1.6)	0.159
Mitral peak late diastolic flow velocity (A) in cm/sec	8.5 (4.1, 12.9)	<0.001	13.3 (8.2, 18.5)	<0.001	-8.1 (-12.6, -3.6)	<0.001	-3.3 (-7.6, 1.1)	0.142	4.9 (-1.1, 10.8)	0.107
E/e'	0.7 (0.1, 1.2)	0.020	-0.1 (-0.6, 0.3)	0.556	0.3 (-0.1, 0.8)	0.143	-0.5 (-0.9, -0.1)	0.026	-0.8 (-1.4, -0.2)	0.006
Tissue Doppler early diastolic flow velocity (e'), cm/sec	-1.1 (-1.9, -0.3)	0.007	-0.03 (-1.0, 0.3)	0.321	-0.1 (-0.7, 0.6)	0.837	0.7 (0.1, 1.3)	0.026	0.8 (-0.1, 1.6)	0.070
Tissue Doppler late diastolic flow velocity (A'), cm/sec	-0.2 (-0.7, 0.3)	0.469	-0.1 (-0.7, 0.4)	0.701	-0.01 (-0.5, 0.5)	0.970	0.1 (-0.4, 0.5)	0.720	0.1 (-0.5, 0.7)	0.767
Isovolumic relaxation time, msec	4.5 (-2.1,11)	0.178	-1.0 (-6.1, 4.1)	0.708	-1.1 (-6.8, 4.6)	0.704	-6.6 (-12.1, -1.1)	0.019	-5.5 (-13, 2.0)	0.153
Isovolumic contraction time, msec	-1.1 (-6.1, 4.1)	0.687	-2.6 (-8.1, 2.8)	0.348	-0.7 (-5.8, 4.4)	0.795	-2.2 (-7.2, 2.7)	0.374	-1.6 (-8.3, 5.1)	0.647
Left atrial volume indexed for body surface area	-0.8 (-3.0, 1.4)	0.488	-1.9 (-4.1, 0.2)	0.083	0.7 (-1.2, 2.7)	0.459	-0.4 (-2.3,1.5)	0.691	-1.1 (-3.6, 1.4)	0.385
Left atrial area, cm^2	0.2 (-0.7, 1.1)	0.651	-0.8 (-1.7, 0.1)	0.089	1.4 (0.6, 2.2)	<0.001	0.4 (-0.4, 1.1)	0.316	-1.0 (-2.0, 0.03)	0.057
Left ventricular systolic indices										
Myocardial performance index	0.03 (-0.01, 0.1)	0.132	0.01(-0.02, 0.04)	0.524	-0.1 (-0.1, -0.03)	<0.001	-0.1 (-0.1, -0.1)	<0.001	-0.02 (-0.1, 0.02)	0.344
Tissue Doppler systolic flow velocity (S), cm/sec	-0.6 (-1.1, -0.02)	.0423	0.2(-0.4, 0.7)	0.543	-0.4 (-0.9, 0.1)	.0877	0.3 (-0.1, 0.8)	0.175	0.7 (0.1, 1.3)	0.019
Global longitudinal systolic function, %	1.14 (0.2, 2.0)	0.013	2.0 (1.0, 2.9)	<0.001	-1.8 (-2.7, -0.9)	<0.001	-0.9 (-1.8, -0.1)	0.035	0.8 (-0.4, 2.0)	0.180
Global circumferential strain %	1.2 (-0.4, 2.78)	0.134	0.6 (-1.1, 2.3)	0.464	-1.3 (-2.9, 0.4)	0.143	-1.8 (-3.5, -0.2)	0.033	-0.6 (-2.8,1.7)	0.616
Ejection fraction, %	-1.5 (-3.9, 0.8)	0.207	-1.5 (-3.7, 0.7)	0.183	3.1(1.0, 5.2)	0.003	3.1 (1.1, 5.1)	0.003	0.003 (-2.7,2.7)	0.998
Hemodynamic parameters										
Peripheral vascular resistance in dynes/sec	56.9 (-50.7, 164)	0.300	22.2 (-79, 123)	0.667	-57.5 (-153, 37.6)	0.236	-92.2 (-184, -0.7)	0.048	-34.6 (-158, 89)	0.583
Cardiac output in L/min	-0.1 (-0.4, 0.3)	0.798	0.1 (-0.3, 0.4)	0.664	0.2 (-0.1, 0.5)	0.258	0.3 (-0.001, 0.6)	0.050	0.1 (-0.3, 0.6)	0.565
Left ventricular structure										
Left ventricular mass indexed for body surface area	2.5 (-2.1, 7.1)	0.285	-0.9 (-4.7, 3.0)	0.649	-3.9 (-7.9, -0.006)	0.050	-7.3 (-11.2, -3.5)	<0.001	-3.4 (-8.6, 1.8)	0.200

Abbreviations: GDM = Gestational diabetes mellitus



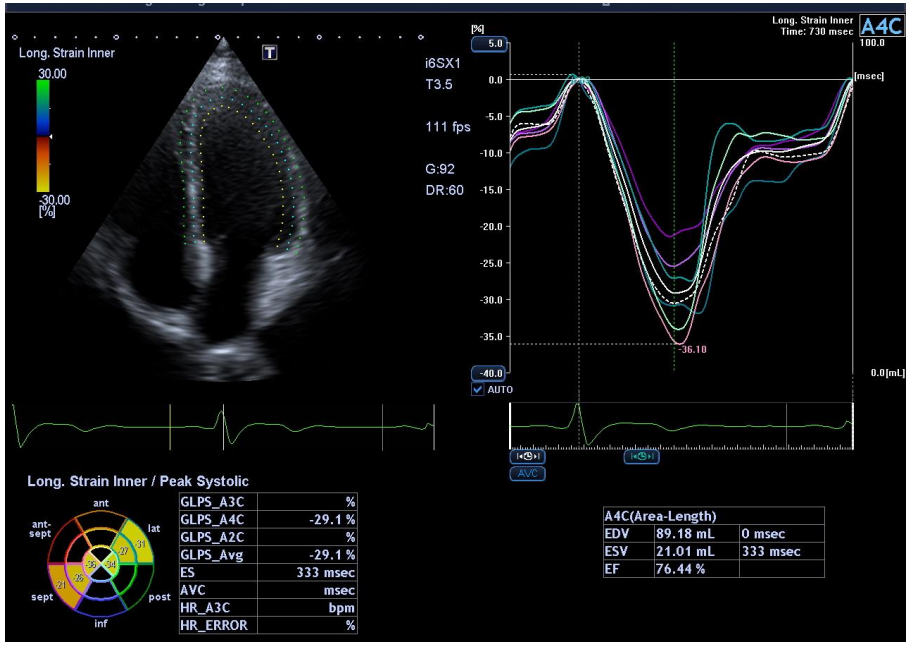


Figure 1

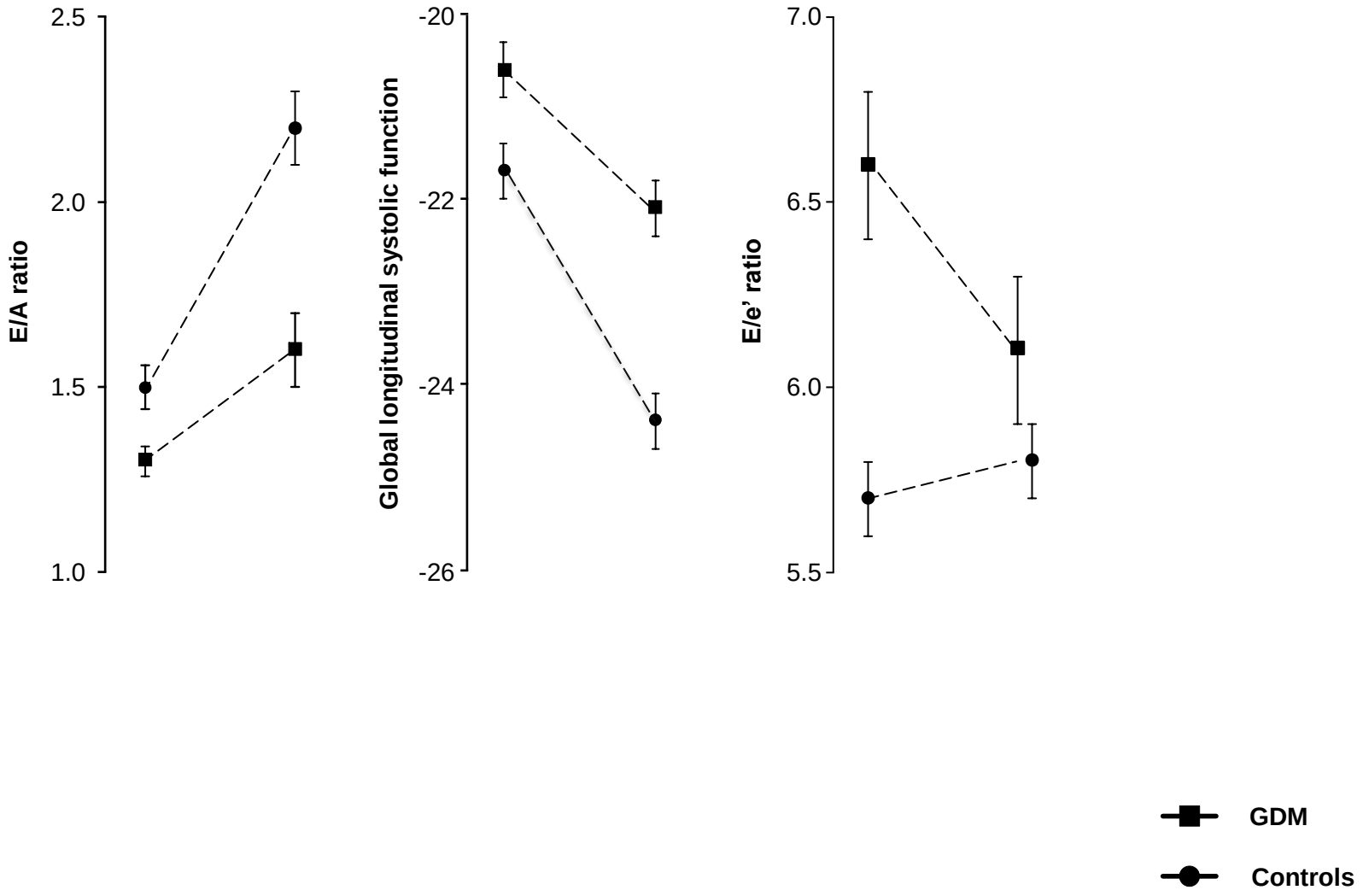


Figure 2