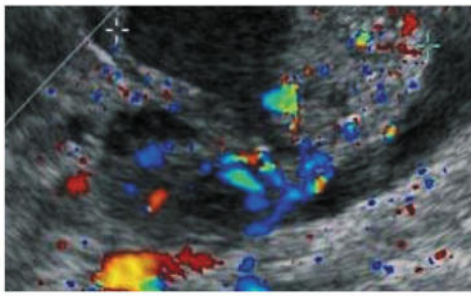
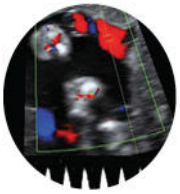
ISUOG Education 2019/20



ISUOG delivers quality education courses internationally in Ultrasound in Obstetrics and Gynecology, providing up-to-date research and clinical guidance for a range of topics and professional levels. Our courses are dynamic, interactive and provide delegates with practical tips as well as excellent networking opportunities.

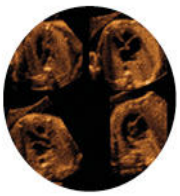


Modern management in twins: All you need to know

4 February 2020
Texas, USA and live streamed worldwide

Course Chairs: Lorraine Dugoff (USA), Asma Khalil (UK), Magda Sanz (USA), Joanne Stone (USA)

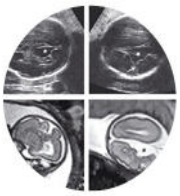
In association with Society for Maternal-Fetal Medicine



Advances in fetal echocardiography

21-22 February 2020
London, UK and live streamed worldwide

Course Chairs: Dario Paladini (Italy), Julene Carvalho (UK)



State of the art ultrasound in pregnancy

16 - 18 April 2020
Washington, USA and live streamed worldwide

Course Chairs: Lorraine Dugoff (USA), Aris Papageorghiou (UK), Laurent Salomon (France), Lynn Simpson (USA), Joanne Stone (USA)

In association with Society for Maternal-Fetal Medicine

Please note the speakers are subject to change at any time.

ISUOG EDUCATION ISUOG EDUCATION ISUOG EDUCATION ISUOG EDUCATION
isuog.org

Our previous delegates said:

"Very relevant to clinical practice"

"Well organised, good speakers"

"Great course, especially the fact that it was live streamed"

Register now at: isuog.org/events

Discounts available for ISUOG members

Find out more at **isuog.org/events.html**
congress@isuog.org | +44 (0)20 7471 9955

isuog.org

The impact of gestational diabetes on maternal cardiac adaptation to pregnancy

Bigna S. Buddeberg[1], MD
Rajan Sharma[2]; BSc (Hons), MD, FRCP (UK), FESC, MBBS
Jamie M. O'Driscoll[2,3]; BSc (Hons), MSc (Hons), PhD
Andrea Kaelin Agten[4,5]; MD
Asma Khalil[4,5]; MBBCH, MD, MRCOG, MSc (Epi), DFSRH, DIP (GUM)
Baskaran Thilaganathan[4,5]; MD, PhD, FRCOG

1. Department of Anesthesiology, University Hospital Basel, Basel, Switzerland
2. Department of Cardiology, St George's University Hospitals NHS Foundation Trust, London, UK.
3. School of Human and Life Science, Canterbury Christ Church University, Kent, UK
4. Fetal Medicine Unit, St George's University Hospitals NHS Foundation Trust, London, UK
5. Molecular & Clinical Sciences Research Institute, St George's University of London, UK

Address for correspondence:
Dr Bigna S. Buddeberg
Department of Anesthesiology, University Hospital Basel
Spitalstrasse 21
CH-4031 Basel, Switzerland
E-mail: bigna.buddeberg@usb.ch

Short title: Cardiac adaptation in diabetic pregnancy

Keywords: Pregnancy, Gestational Diabetes, Echocardiography, Speckle Tracking, Cardiac Dysfunction, Diastolic Dysfunction

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/uog.21941

CONTRIBUTION

What are the novel findings of this work?

This is the first prospective study of comprehensive echocardiographic assessment including left and right ventricular geometry and function in women with gestational diabetes. We demonstrate that even a short duration of exposure to hyperglycaemia leads to echocardiographic changes comparable to those seen in non-pregnant diabetes mellitus.

What are the clinical implications of this work?

The echocardiographic findings in gestational diabetes may explain the increased maternal risk to hypertensive disorders of pregnancy and cardiovascular disease later in life.

ABSTRACT

Objectives: To determine whether maternal cardiac adaptation at term differs in women with and without gestational diabetes (GDM).

Methods: This was a prospective case-control study of pregnant women at term with and without GDM. Conventional as well as speckle tracking echocardiography was used to assess both left and right heart geometry and function.

Results: We enrolled a total of 40 women with GDM and 40 healthy controls. Heart rate (75±9 vs 83±10; p<0.001), left ventricular (LV) relative wall thickness (0.37±0.08 vs 0.43±0.07; p<0.001), LV E (early diastolic trans-mitral valve velocity) (0.73±0.12 vs 0.80±0.15; p=0.26) and LV A (late diastolic trans-mitral valve velocity) (0.57±0.11m/s vs 0.65±0.13m/s; p=0.006) were significantly raised in GDM compared to controls. Speckle tracking analysis revealed a significant reduction in LV global longitudinal strain (-17.61±1.89 vs -16.29±2.26; p=0.012), LV endocardial global longitudinal strain (-19.84±2.35 vs -18.5±2.59; p=0.031) and LV epicardial longitudinal global strain (-15.73±1.66 vs -14.40±2.01; p=0.005) in GDM. Right ventricular (RV) analysis revealed reduced pulmonary acceleration time (66±11ms vs 58±10ms; p=0.001) , RV E/A ratio (1.29±0.35 vs 1.13±0.18; p=0.017), RV A (0.39±0.08m/s vs 0.46±0.1m/s; p=0.001) as well as higher RV S' (myocardial systolic annular velocity) (0.14±0.02 vs 0.16±0.04; p=0.023) in GDM.

Conclusion: Even a short period of exposure to hyperglycaemia as occurs in GDM, is associated with significant maternal functional cardiac impairment at term. Given the established increased post-partum cardiovascular risk after GDM, consideration should be given to further study of the extent of postnatal maternal cardiovascular recovery after GDM pregnancy.

INTRODUCTION

Gestational diabetes (GDM) is hyperglycaemia with onset or diagnosis in pregnancy and occurs in one out of seven pregnancies.[1,2] GDM is associated with adverse perinatal outcomes for both the mother and the fetus.[2, 3] Women whose pregnancies were complicated with GDM have a more than seven-fold higher incidence of type 2 diabetes later in life.[4] A recent meta-analysis of nine studies pooling data from more than 5 million women, demonstrated that women who had GDM also have a two-fold higher risk of cardiovascular events in the first decade postpartum.[5] The effect of long standing diabetes mellitus (DM) on the adult heart is well documented, with a wide spectrum of dysfunction including diabetic cardiomyopathy.[6] Various microvascular processes and subcellular disturbances have been shown to cause structural and functional damage to the diabetic heart, even without overt coronary artery disease.[7]

In contrast, very little is known about the impact of short term hyperglycaemia on the heart as occurs in GDM. There is a lack of prospective studies examining how GDM influences maternal cardiac adaptation to the increasing cardiovascular demands of pregnancy.[8-13] The aim of the present study is to compare maternal cardiac adaptation at term in women with and without GDM. We hypothesized that the duration of hyperglycaemia in GDM pregnancy is not long enough to result in cardiovascular differences assessed using conventional echocardiography and speckle tracking to study left and right heart function.

METHODS

This prospective case-control study was carried out at St. George's University Hospitals NHS Foundation Trust in London over a 12-month period from April 2016 until March 2017. The local institutional review committee approved the study (ID 12/LO/0810) and all participants provided written informed consent. We recruited pregnant women at term that had a pathological oral glucose tolerance test by 28 weeks of gestation and were classified as having gestational diabetes. The oral glucose tolerance test was carried out according to national guidelines. A fasting blood sugar was taken, and then the women received a glucose load of 75g. After 2 hours, blood glucose was determined again. Cut off values for GDM were a fasting blood sugar level of ≥5.6mg/dl or a 2-hour value of ≥7.8mg/dl.[3] Women who were managed with diet only as well as those who received oral hypoglycemic or insulin were included. Only women without any cardiovascular co-morbidities or any form of preexisting diabetes (type I, type II) were asked to take part in the study. Healthy term pregnant women with a BMI of 30kg/m^2 or less at booking and without any co-morbidity were recruited as controls. For both cases and controls, only women with a singleton pregnancy without pregnancy complications (such as preeclampsia or fetal growth restriction) were considered. Blood pressure was measured manually from the brachial artery according to the guidelines of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy.[14]

Conventional echocardiography and speckle tracking echocardiography

Echocardiography examination and analysis were performed by a single operator (BSB) using a GE Vivid Q® ultrasound machine equipped with a 3.5-MHz transducer. Images were acquired at rest in the left lateral decubitus position from standard parasternal and apical views. Digital loops of 3 cardiac cycles with associated electrocardiogram information were stored on the hard disk of the ultrasound machine and transferred to a GE EchoPac® workstation for offline analysis. Analysis was performed according to existing guidelines and as previously described.[15-17] Parasternal long-axis, short-axis and apical four chamber views

were used to assess left atrial volume (LAV), left ventricular volume in diastole (LVEDV), proximal and distal right ventricular outflow tract (RVOT) as well as other geometric indices. Doppler images were used to measure early and late mitral and tricuspid valve inflow velocities (LV and RV E and A), mitral and tricuspid inflow deceleration time (LV and RV DT), isovolumetric relaxation time (IVRT) and duration of the late mitral valve inflow (A dur). Left ventricular mass was calculated using the Devereux formula $0.8(1.04[([LVEDD + IVSd + PWd]^3 - LVEDD^3)]) + 0.6v$, where LVEDD is left ventricular end diastolic diameter, IVSd is thickness of the intraventricular septum in diastole and PWd is posterior wall thickness in diastole. Left ventricular mass index was calculated by deviding the left ventricular mass by the body surface area. Relative left ventricular wall thickness was calculated with the formula (2*PWd)/LVEDD.

Pulsed wave tissue Doppler images were used to measure systolic (S'), early diastolic (E') and late diastolic (A') myocardial tissue velocities at the basal level of the septum and left and right ventricular walls. LV and RV longitudinal strain and systolic and diastolic (early and late) strain rates were calculated from apical four chamber views, with negative values indicating fiber shortening. LV rotation and de-rotation were calculated from apical and basal parasternal short axis views, with negative values indicating rotation in the clockwise direction. LV twist is the difference between the apical and the basal rotation, LV torsion is LV twist divided by left ventricular length in diastole. If >1 segment was rejected, subjects were excluded from statistical analysis. Diastolic dysfunction was classified according to the guidelines of the British Society of echocardiography applying the age and gender adapted values from the 2016 European Society of Cardiology Guidelines for the diagnosis and treatment of acute and chronic heart failure.[18, 19]

Statistical analysis

Descriptive statistics were performed. Continuous data were presented as mean (standard deviation, SD). Normal distribution was assessed using Shapiro-Wilk test. Categorical data

were presented as number (%) and were compared using the Chi square test. Comparisons between the groups were performed using either unpaired t-test or Mann Whitney U test for continuous data, depending on distribution of data. IBM SPSS statistics version 24 was used ($p<0.05$ considered as significant). Intra- and interobserver variablility has been performed as previously described by our group[20] and was not repeated in this study.

RESULTS

We enrolled a total of 80 pregnant women at term, 40 women with GDM and 40 healthy women. Conventional echocardiography evaluation of the left ventricle could be performed in all women, but speckle-tracking analysis could not be performed in four controls and seven GDM women. Demographic characteristics of the control and GDM groups are shown in Table 1. GDM women had a significantly higher BMI and a higher systolic blood pressure at booking and at inclusion into the study compared to controls.

Echocardiographic indices were not significantly different between the two groups (Table 2) with the exception of the heart rate, relative left ventricular wall thickness, left ventricular E (early diastolic trans-mitral valve velocity) and A (late diastolic trans-mitral valve velocity), which were significantly raised in GDM. Of special note is that left ventricular mass and left ventricular mass index did not differ significantly between groups. Longitudinal strain analysis of the left ventricle showed significant reduction in global strain, endocardial global strain and epicardial global strain in GDM pregnancies (Figure1). Right ventricular analysis revealed reduced pulmonary acceleration time and RV E/A ratio as well as higher RV S' (myocardial systolic annular velocity) and RV A in the GDM population. Speckle tracking analysis of the right ventricle did not reveal any differences between the control and the GDM group (Supplementary Table A).

DISCUSSION

Women with GDM at term had a significantly impaired cardiac function compared to healthy control pregnancies as demonstrated by significantly increased left ventricular relative wall thickness and reduced longitudinal left ventricular global strain, longitudinal left ventricular endocardial and longitudinal epicardial global strain. These subclinical changes suggest a significantly maladaptive cardiovascular response in apparently uncomplicated term GDM pregnancy.

Outside pregnancy, Enomoto *et al.* studied systolic dysfunction with speckle tracking in normotensive diabetic patients and found a reduction in global longitudinal and subendocardial strain.[21] However, the effect of diabetes on the heart is confounded by the common co-existence of metabolic syndrome, where the effect on cardiac function is influenced not only by diabetes, but also hypertension and dyslipidaemia. Studies assessing cardiac changes in metabolic syndrome also found decreased longitudinal and circumferential strain in the left ventricle[22, 23] and decreased global longitudinal strain in the right ventricle.[24] It is notable that exposure of the maternal heart to a short period of hyperglycaemia parallels the cardiac dysfunction seen in non-pregnant patients after decades of diabetes. There is one previous retrospective study of 18 pregnant women with GDM at the end of the second trimester. The authors demonstrated differences only in global longitudinal strain with preserved circumferential and radial strain in GDM.[25] Although this data supports the findings of the present study, the lack of additional cardiovascular findings may be explained by the retrospective nature of the study, smaller sample size, reduced loading conditions of earlier gestation of assessment and a shorter period of exposure to hyperglycaemia. Two prospective conventional echocardiographic studies found an increase in left ventriuclar wall thickness and decreased diastolic function supporting our findings.[11, 12]

GDM is a strong risk factor for the development of hypertensive disorders of pregnancy and fetal growth[26, 27] – both pathologies where recent work has shown significant deficits in maternal cardiovascular function[28, 29]. By deliberately excluding GDM pregnancies that developed these complications from our study, we may have inadvertently introduced exclusion bias by not studying women who developed cardiac dysfunction as a consequence of these pregnancy complications. Hence, our data is more reflective of the cardiac function in apparently 'healthy' GDM pregnancy rather than showing the evolution of more severe cardiac dysfunction as has been shown to occur with the development of preeclampsia or fetal growth restriction[28, 29]. Despite these exclusions, it is notable that the prevalence of diastolic dysfunction is 2.8-fold higher in GDM compared to normal pregnancy at term. The latter observation has previously been implicated in the development of hypertensive disorders of pregnancy.

The mechanism by which diabetes causes cardiac dysfunction outside pregnancy are not entirely understood and the spectrum of diabetic cardiovascular effects including myocardial fibrosis, remodeling, diastolic dysfunction and later systolic dysfunction are commonly described as diabetic cardiomyopathy. Impaired cardiac insulin signaling, mitochondrial dysfunction, oxidative stress, advanced glycation, cardiomyocyte calcium handling, inflammation, renin–angiotensin–aldosterone system activation and microvascular dysfunction have all been implicated in the development and progression of diabetic cardiomyopathy, myocardial damage and subsequent fibrosis[30, 31]. A recent meta-analysis found that women who had GDM during pregnancy have a two-fold higher risk of cardiovascular events in the first decade postpartum, independent of whether or not they develop postpartum type II diabetes.[5] The authors postulated that GDM, like preeclampsia, may unmask during pregnancy those women who have a higher postpartum cardiovascular risk[29, 32, 33]. It would be interesting to postulate that the pathophysiology of cardiovascular dysfunction in GDM pregnancy may lead to long-term myocardial damage and fibrosis as is known to occur in diabetic cardiomyopathy. Future studies should evaluate postpartum

cardiovascular function after GDM pregnancy and determine whether persistent myocardial dysfunction is caused by GDM pregnancy alone or is confounded by the effects of other cardiovascular risk factors.

Strength and limitations

The strengths of our study are that it is prospective in design and assessed both left and right heart function using conventional as well as speckle tracking echocardiography to evaluate cardiac function. The weakness of our study is that women who developed GDM also had a higher booking BMI and systolic blood pressure. It is not possible to delineate to what extent the former factors may have influenced the development of the cardiovascular dysfunction noted in GDM pregnancy. Reassuringly, our previous work demonstrated maternal cardiovascular dysfunction in non-diabetic pregnancy with BMI>35kg/m^2, which is substantially higher than the BMI of our GDM population. Pregnant women with a BMI>35kg/m^2 had a significantly higher SV, CO and LVM and a significantly lower TVR. If corrected for maternal weight, the differences disappeared except for LVMI. The GDM group showed no difference in SV, SVI, CO, CI, LVM, LVMI, TVR and TVRI compared to controls. We therefore feel confident to relate the observed differences in speckle tracking and in diastolic dysfunction to the presence of GDM and not to the higher BMI in the GDM group. Interestingly, diastolic dysfunction, if present, was more severe in GDM pregnancy than in the obese pregnancy. Furthermore, women in the GDM group were, on average, scanned two weeks earlier than the control group. As maternal cardiac maladaptation increases with advancing gestation, the latter difference would have only served to ameliorate, rather than exaggerate, any differences between GDM and normal pregnancy.[8]

Conclusion

A short period of exposure to hyperglycaemia as occurs in GDM, is associated with significant maternal functional cardiac impairment at term. Given the established increased post-partum

cardiovascular risk after GDM, consideration should be given to further study of the extent of postnatal maternal cardiac recovery after GDM pregnancy.

ACKNOWLEDGEMENTS

We are grateful to the midwives and sonographers of the Fetal Maternal Medicine Unit at St. George's Hospital, for their invaluable effort to help with patient recruitment.

SOURCES OF FUNDING

Dr Bigna Buddeberg was funded by Foundation Prof. Max Cloëtta/Uniscientia Foundation and the "Stiftung Anästhesiologie und Intensivmedizin Basel" from the University in Basel. The sponsors did not have any involvement in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

Prof Basky Thilaganathan is supported by funds from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No. 765274 (www.iplacenta.eu).

DECLARATION OF INTEREST

None

REFERENCES

1. Loubeyre P, Petignat P, Jacob S, Egger JF, Dubuisson JB, Wenger JM. Anatomic distribution of posterior deeply infiltrating endometriosis on MRI after vaginal and rectal gel opacification. *AJR Am J Roentgenol* 2009; **192**: 1625-1631.
2. Piper LK, Stewart Z, Murphy HR. Gestational diabetes. *Obstet Gynecol and Reprod Med* 2017; **27**: 171-176.
3. Johns EC, Denison FC, Norman JE, Reynolds RM. Gestational Diabetes Mellitus: Mechanisms, Treatment, and Complications. *Trends Endocrinol Metab* 2018; **29**: 743-754.
4. Bellamy L, Casas JP, Hingorani AD, Williams D. Type 2 diabetes mellitus after gestational diabetes: a systematic review and meta-analysis. *Lancet* 2009; **373**: 1773-1779.
5. 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.
6. Singh RM, Waqar T, Howarth FC, Adeghate E, Bidasee K, Singh J. Hyperglycemia-induced cardiac contractile dysfunction in the diabetic heart. *Heart Fail Rev* 2018; **23**: 37-54.
7. Lee WS, Kim J. Diabetic cardiomyopathy: where we are and where we are going. *Korean J Intern Med* 2017; **32**: 404-421.
8. 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.
9. 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. DOI:10.1002/uog.20170.
10. Buddeberg BS, Sharma R, O'Driscoll JM, Kaelin Agten A, Khalil A, Thilaganathan B. Cardiac maladaptation in term pregnancies with preeclampsia. *Pregnancy Hypertens* 2018; **13**: 198-203.
11. Oliveira AP, Calderon IM, Costa RA, Roscani MG, Magalhaes CG, Borges VT. Assessment of structural cardiac abnormalities and diastolic function in women with gestational diabetes mellitus. *Diab Vasc Dis Res* 2015; **12**: 175-180.
12. Zakovicova E, Charvat J, Mokra D, Svab P, Kvapil M. The optimal control of blood glucose is associated with normal blood pressure 24h profile and prevention of the left ventricular remodeling in the patients with gestational diabetes mellitus. *Neuro Endocrinol Lett* 2014; **35**: 327-333.
13. Osman MW, Nath M, Khalil A, Webb DR, Robinson TG, Mousa HA. Haemodynamic differences amongst women who were screened for gestational diabetes in comparison to healthy controls. *Pregnancy Hypertens* 2018; **14**: 23-28.
14. Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy. *Am J Obstet Gynecol* 2000; **183**: s1-s22.
15. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD, Spencer KT, Sutton MS, Stewart WJ, Chamber Quantification Writing G, American Society of Echocardiography's G, Standards C, European Association of E. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr* 2005; **18**: 1440-1463.
16. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF, 3rd, Dokainish H, Edvardsen T, Flachskampf FA, Gillebert TC, Klein AL, Lancellotti P, Marino P, Oh JK, Alexandru Popescu B, Waggoner AD, Houston T, Oslo N, Phoenix A, Nashville T, Hamilton OC, Uppsala S, Ghent, Liege B, Cleveland O,

Novara I, Rochester M, Bucharest R, St. Louis M. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2016; **17**: 1321-1360.
17. Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, Solomon SD, Louie EK, Schiller NB. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. *J Am Soc Echocardiogr* 2010; **23**: 685-713; quiz 786-688.
18. Mathew T, Steeds R, Jones R, Kanagala P, Lloyd G, Knight D, O'Gallagher K, Oxborough D, Rana B, Ring L, Sandoval J, Wharton G, Wheeler R. A Guideline Protocol for the Echocardiographic Assessment of Diastolic Dysfunction. *The British Society of Echocardiography Education Committee* 2013.
19. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P, Group ESCSD. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2016; **37**: 2129-2200.
20. Melchiorre K, Sutherland GR, Baltabaeva A, Liberati M, Thilaganathan B. Maternal cardiac dysfunction and remodeling in women with preeclampsia at term. *Hypertension* 2011; **57**: 85-93.
21. Enomoto M, Ishizu T, Seo Y, Yamamoto M, Suzuki H, Shimano H, Kawakami Y, Aonuma K. Subendocardial Systolic Dysfunction in Asymptomatic Normotensive Diabetic Patients. *Circ J* 2015; **79**: 1749-1755.
22. Tadic M, Cuspidi C, Majstorovic A, Pencic B, Backovic S, Ivanovic B, Scepanovic R, Martinov J, Kocijancic V, Celic V. Does the metabolic syndrome impact left-ventricular mechanics? A two-dimensional speckle tracking study. *J Hypertens* 2014; **32**: 1870-1878.
23. Crendal E, Walther G, Vinet A, Dutheil F, Naughton G, Lesourd B, Chapier R, Rupp T, Courteix D, Obert P. Myocardial deformation and twist mechanics in adults with metabolic syndrome: impact of cumulative metabolic burden. *Obesity (Silver Spring)* 2013; **21**: E679-686.
24. Tadic M, Cuspidi C, Sljivic A, Andric A, Ivanovic B, Scepanovic R, Ilic I, Jozika L, Marjanovic T, Celic V. Effects of the metabolic syndrome on right heart mechanics and function. *Can J Cardiol* 2014; **30**: 325-331.
25. Meera SJ, Ando T, Pu D, Manjappa S, Taub CC. Dynamic left ventricular changes in patients with gestational diabetes: A speckle tracking echocardiography study. *J Clin Ultrasound* 2017; **45**: 20-27.
26. Carr DB, Newton KM, Utzschneider KM, Faulenbach MV, Kahn SE, Easterling TR, Heckbert SR. Gestational diabetes or lesser degrees of glucose intolerance and risk of preeclampsia. *Hypertens Pregnancy* 2011; **30**: 153-163.
27. Hauth JC, Clifton RG, Roberts JM, Myatt L, Spong CY, Leveno KJ, Varner MW, Wapner RJ, Thorp Jr JM, Mercer BM, Peaceman AM, Ramin SM, Carpenter MW, Samuels P, Sciscione A, Tolosa JE, Saade G, Sorokin Y, Anderson GD, Network. EKSNIoCHaHDM-FMU. Maternal insulin resistance and preeclampsia. *Am J Obstet Gynecol* 2011; **204**: 327.e321-326.

28. Melchiorre K, Sutherland GR, Liberati M, Thilaganathan B. Maternal cardiovascular impairment in pregnancies complicated by severe fetal growth restriction. *Hypertension* 2012; **60**: 437-443.
29. Thilaganathan B, Kalafat E. Cardiovascular System in Preeclampsia and Beyond. *Hypertension* 2019; **73**: 522–531.
30. Lorenzo-Almoros A, Tunon J, Orejas M, Cortes M, Egido J, Lorenzo O. Diagnostic approaches for diabetic cardiomyopathy. *Cardiovasc Diabetol* 2017; **16**: 28.
31. Jia G, Hill MA, Sowers JR. Diabetic Cardiomyopathy: An Update of Mechanisms Contributing to This Clinical Entity. *Circ Res* 2018; **122**: 624-638.
32. Melchiorre K, Sutherland GR, Liberati M, Thilaganathan B. Preeclampsia is associated with persistent postpartum cardiovascular impairment. *Hypertension* 2011; **58**: 709-715.
33. Behrens I, Basit S, Melbye M, Lykke JA, Wohlfahrt J, Bundgaard H, Thilaganathan B, Boyd HA. Risk of post-pregnancy hypertension in women with a history of hypertensive disorders of pregnancy: nationwide cohort study. *BMJ* 2017; **358**: j:3078.

FIGURE LEGEND

Figure 1: Representative speckle tracking and strain rate analysis in GDM (A, B, C) and control (D, E, F). GSendo = global endocardial strain; GS = global strain; GSepi = global epicardial strain.

Table 1: Demographic characteristics of women with normal and GDM pregnancy			
	Controls (n=40)	**GDM (n=40)**	**p-value**
Maternal age (years)	34.8 (4.0)	33.2 (4.5)	0.099
Ethnicity:			**0.001**
- Caucasian	34 (85.0%)	25 (62.5%)	
- Afro-Caribbean	2 (5.0%)	4 (10.0%)	
- Asian	4 (10.0%)	11 (27.5%)	
Parity:			**<0.001**
- Nulliparous	16 (40.0%)	20 (50.0%)	
- Multiparous	24 (60.0%)	20 (50.0%)	
Booking visit BMI (kg/m^2)	23.7 (2.5)	30.4 (8.0)	**<0.001**
Booking visit SBP (mmHg)	109 (11)	119 (13)	**<0.001**
Booking visit DBP (mmHg)	67 (8)	72 (9)	**0.012**
Gestation at assessment (weeks)	39.3 (1.0)	37.0 (1.3)	**<0.001**
BMI at assessment (kg/m^2)	28.1 (3.0)	32.6 (6.9)	**<0.001**
SBP at assessment (mmHg)	109 (9)	114 (11)	**0.024**
DBP at assessment (mmHg)	74 (8)	74 (9)	0.790

Results are shown as mean (±SD) or number of subjects (percentage). GDM=gestational diabetes; BMI=body mass index; SBP=systolic blood pressure; DBP=diastolic blood pressure

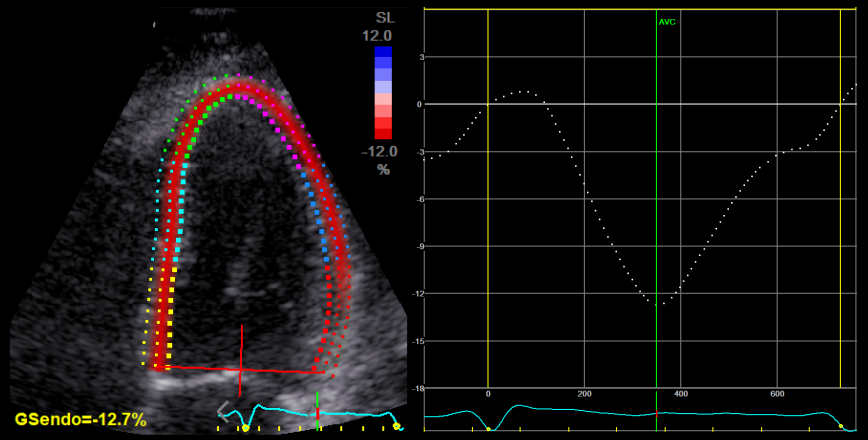
Table 2: Left ventricular hemodynamic, geometric and speckle tracking-derived indices			
	Controls (n=40)	**GDM (n=40)**	**p-value**
Hemodynamic Indices			
HR (min^{-1})	75 (9)	83 (10)	**<0.001**
SV (ml)	66 (11)	64 (13)	0.346
SVI ($ml*m^{-2}$)	36 (6)	34 (7)	0.143
CO ($ml*min^{-1}$)	4896 (849)	5295 (1239)	0.163
CI ($ml*min*m^{-2}$)	2664 (439)	2797 (537)	0.227
TVR ($dynes*s^{-1}*cm^{-5}$)	1448 (332)	1390 (347)	0.448
TVRI ($dynes*s^{-1}*cm^{-5}*m^{-2}$)	2658 (605)	2605(634)	0.704
Average S' (m/s)	0.10 (0.02)	0.10 (0.02)	0.746
Geometric Indices			
LAV (ml)	55 (12)	57 (14)	0.507
LAVI ($ml*m^{-2}$)	30 (6)	30 (7)	0.877
LVM (g)	119 (21)	128 (36)	0.172
LVMI ($g*m^{-2}$)	64 (10)	67 (13)	0.365
RWT	0.37 (0.08)	0.43 (0.07)	**<0.001**
Mitral inflow indices			
E (m/s)	0.73 (0.12)	0.80 (0.15)	**0.026**
A (m/s)	0.57 (0.11)	0.65 (0.13)	**0.006**
E/A ratio	1.28 (0.18)	1.26 (0.30)	0.699
Septal E' (m/s)	0.10 (0.03)	0.10 (0.02)	0.567
Lateral E' (m/s)	0.15 (0.04)	0.15 (0.03)	0.843
E/E' average	6.18 (1.57)	7.02 (2.82)	0.103
Diastolic function			
Normal	35 (87.5)	26 (65)	**0.010**
Grade 1 Diastolic Dysfunction	4 (10)	2 (5)	

Grade 2 Diastolic Dysfunction	1 (2.5)	12 (30)	
Grade 3 Diastolic Dysfunction	0 (0)	0 (0)	

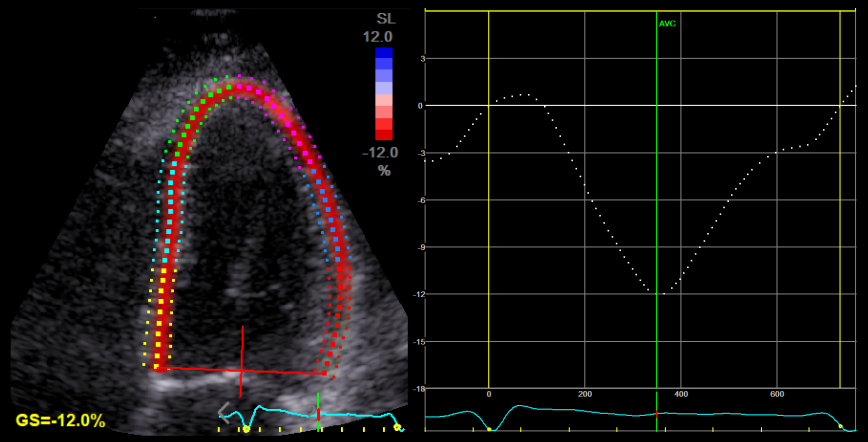
Strain and strain rate indices			
LV global strain (%)	-17.61 (1.89)	-16.29 (2.26)	**0.012**
LV endocardial global strain (%)	-19.84 (2.35)	-18.50 (2.59)	**0.031**
LV epicardial global strain (%)	-15.73 (1.66)	-14.40 (2.01)	**0.005**
LV longitudinal strain rate (s^{-1})	-0.98 (0.12)	-0.96 (0.15)	0.509
LV early diastolic strain rate (s^{-1})	1.24 (0.26)	1.15 (0.32)	0.235
LV late diastolic strain rate (s^{-1})	0.55 (0.16)	0.60 (0.19)	0.302
Twist and torsion indices			
LV twist (degree)	14.33 (5.69)	16.39 (6.69)	0.223
LV torsion (degree*cm^{-1})	1.66 (0.66)	1.88 (0.76)	0.252
LV twist rate (degree*s^{-1})	102 (48)	134 (55)	**0.048**
LV un-twist rate (degree*s^{-1})	-106 (56)	-125 (47)	0.194

Results are shown as mean (±SD). HR=heart rate; SV=stroke volume; SVI=stroke volume index; CO=cardiac output; CI=cardiac index; TVR=total vascular resistance; TVRI=total vascular resistance index; Average S'=systolic tissue Doppler average velocity at the septal/lateral mitral valve annulus; LAV=left atrial volume; LAVI=left atrial volume index; LVM=left ventricular mass; LVMI=left ventricular mass index; RWT=relative left ventricular wall thickness; E=peak early diastolic transmitral valve velocity; A=peak late diastolic transmitral valve velocity; Septal/lateral E'=peak early diastolic tissue Doppler velocity at the septal/lateral mitral valve annulus; E/E' average=E to average lateral and septal E' ratio

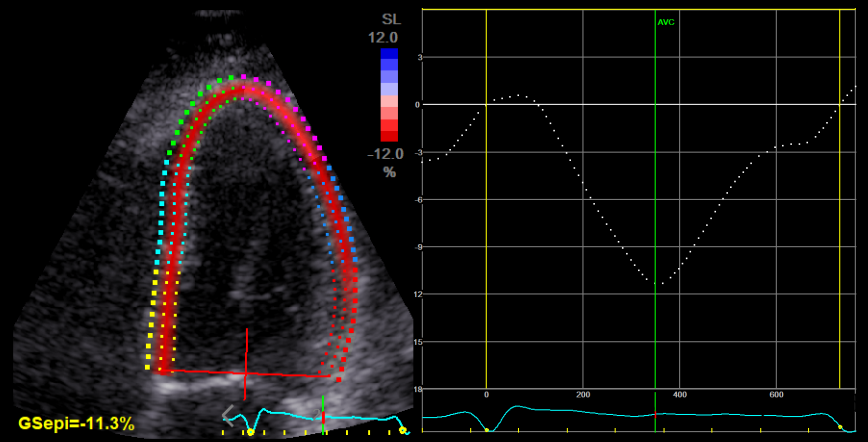
A



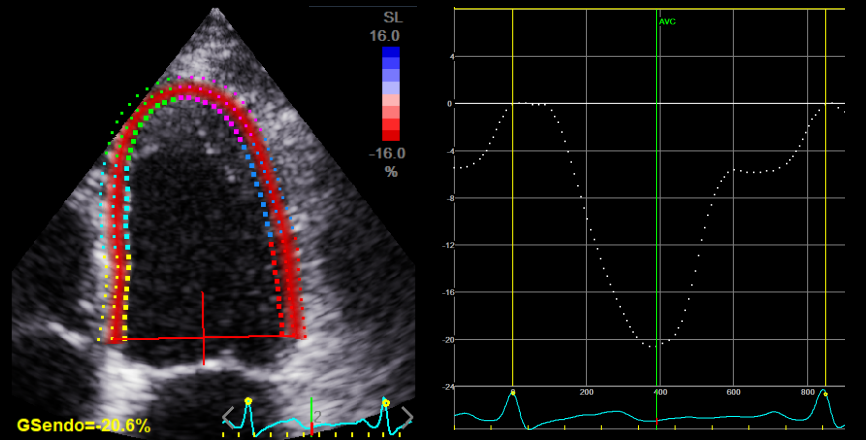
B



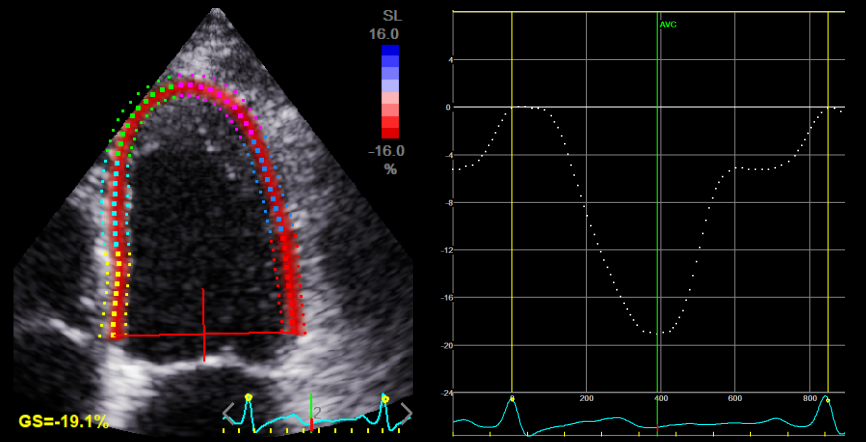
C



D



E



F