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Left Ventricular Systolic Function in Pregnant Women with Inherited Thrombophilia

Livia Florentina TRASCA[a], Elena POENARU[a], Natalia PATRASCU[a], Ramona BRUJA[b], Octavian MUNTEANU[a], Monica CIRSTOIU[a], Dragos VINEREANU[a]

[a]"Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

[b]"Victor Babes" Clinical Hospital, Bucharest, Romania

ABSTRACT

Objectives: *The impact of the gestational changes on left ventricular contractility is not clearly defined. Our aim was to evaluate the subtle changes of left ventricular systolic function during pregnancy, assessed by new echocardiographic techniques, in a population tested for inherited thrombophilia.*

Material and methods: *Eighty seven consecutive pregnant women, with a mean age of 32±4 years, genetically tested for inherited thrombophilia (22 with thrombophilic mutations and risk of thrombosis and 65 without significant mutations, considered as the control group) were included. All participants had four clinical and echocardiographyc visits: three during pregnancy (one in each trimester) and the forth six months after giving birth. Left ventricular (LV) systolic function was assessed from ejection fraction (EF) by 2D and 3D echocardiography, mitral annular velocities by tissue Doppler, and strain rate by 2D speckle tracking.*

Outcomes: *There were no differences between groups for any of the echo parameters at each of the four visits. Comparing the third visit with the first one, all parameters of LV systolic function had significantly lower values at the end of pregnancy; EF decreased from 58% to 55% (2D echo), from 60% to 56% (3D TomTec), and from 58% to 55% (Auto4DLVQ), with p<0.001 for all three methods. Moreover, strain assessed by speckle traking decreased during pregnancy, with no differences between groups. In addition to this, mitral annular velocities obtained by tissue Doppler assessment decreased during the gestational period, with no differences between groups. At six months after giving birth, all values were normalized.*

Conclusion: *During pregnancy, LV contractility has a slight decrease, with no criteria of systolic dysfunction. Thrombophilic mutations, with correct anticoagulant treatment, has no impact on LV systolic function.*

Keywords: pregnancy, contractility, thrombophilia.

Address for correspondence:
Dragos Vinereanu, MD, PhD, FESC, FRCP, FAHA
Emergency University Hospital, 10th Floor (Cardiology), Splaiul Independentei, No. 169, Sector 5, Bucharest, Romania
Tel.: 021.318.05.19
Email: vinereanu@gmail.com

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INTRODUCTION

In normal pregnancy, cardiac performance is overall improved due to hypervolemia and increased heart rate associated with decreased vascular resistance. Despite this generally accepted idea, the impact of gestational changes on cardiac contractility is not clearly defined (1). Anatomic changes of the left ventricle are: increased muscle mass and dilation of the cavity (mild eccentric hypertrophy) with the gestational age. However, data on cardiac systolic function in pregnancy are contradictory. Thus, different studies on left ventricular ejection fraction, assessed by echocardiography, showed decreased, maintained, or increased cardiac contractility (1-3).

Pregnancy is characterized by hypercoagulability through the modified hemostasis at three levels: increased platelet activity, increased procoagulant activity and decreased fibrinolysis activity. Vascular stasis and hypercoagulability may cause endothelial injury, and all these factors augment the risk of thromboembolic events, resulting in a 5 to 7 fold increased risk in pregnant women (4, 5). Moreover, in case of another procoagulant status, like inherited thrombophilia, the risk of thrombotic events is even more augmented. Our aim was to evaluate subtle changes of left ventricular systolic function during pregnancy, assessed by new echocardiographic techniques, in a population tested for inherited thrombophilia. Understanding progressive cardiovascular changes related to high risk thrombophilia in pregnancy is required for an accurate interpretation of the cardiac function during the gestational period, and to predict the effects of pregnancy on the woman with underlying cardiac disease. ❑

MATERIAL AND METHODS

Study population. Between December 2015 and September 2016, 87 consecutive pregnant participants to RO-19.10 registry were included. All women were in sinus rhythm, without known cardiovascular disease or risk factors. This registry had the initial purpose to evaluate the prevalence of inherited thrombophilia among women in Romania. The study protocol was approved by the local Ethics Committee and complied with the Helsinki Declaration (4). Written informed consent was obtained from all participants.

Blood analysis. All women were tested for inherited thrombophilia using venous blood samples in order to detect quantitative disorders and qualitative anomalies (genetic defects) of different factors involved in hemostasis. The analysed tests for thrombophilia are listed in Table 1. Each pregnant woman had at least one thrombophilic mutation. Inherited thrombophilia is defined by the mutation type, number of genetical defects, risk factors, and personal and/or familial history of thrombosis. According to the current guidelines for management of inherited thrombophilia during pregnancy, there are high risk criteria for developing thrombotic events during pregnancy, such as personal history of a thrombotic event associated with any type of inherited thromphilia, homozygous mutation or double heterozygous mutation for factor V Leyden, prothrombin G20210A, or antithrombin III genes (5–7). Considerating all these criteria, we divided the group into two subgroups: one with inherited thrombophilia and thrombotic risk, and the second one representing the control group.

Echocardiography. Study participants had four echocardiographic evaluations, with three of them during pregnancy. The first visit was performed at 15±2 weeks of pregnancy, the second one at 25±2 weeks, the third visit at 35±2 week, and the forth one at 24±2 weeks (six months) after giving birth. Acquisitions were performed in the left lateral decubitus position using a Vivid 9 machine (GE Healthcare, Horten, Norway), equipped with M5S and 4V probes. All images and measurements were obtained from standard

Genetic tests – mutation type (codified protein)	Quantitative tests
• G1691A (Factor V Leiden)	• Antithrombin III
• H1299R (Factor V Leiden)	• Protein C
• G20210A (prothrombin)	• Protein S
• C677T (MTHFR)	• Homocysteine
• A1298C (MTHFR)	• Lupus C
• G103T (Factor III)	• Lupus S
• 4G/5G polymorphism (PAI I)	
• G4600A (EPCR)	
• C4678G (EPCR)	

EPRC = endothelial protein C receptor; PAI = plasminogen activator inhibitor; MTHFR = methylenetetrahydrofolate reductase.

TABLE 1. Tests for thrombophilia

views, according to the current guidelines for chamber quantification (8, 9). Images were digitally stored and analyzed offline using a customized software (EchoPAC, GE Healthcare).

2D echocardiographic analysis allowed the evaluation of left ventricular systolic function using standard parameters (Table 2). Tissue Doppler imaging (TDI) was used to measure the peak longitudinal myocardial velocities (S waves) at the level of the mitral (lateral and medial) annulus. Three consecutive cycles were recorded at a frame rate between 60 and 80 fps, during breath hold, to obtain accurate apical 4C, 2C, and 3C views of the left ventricle, in order to perform a speckle-tracking analysis. Radial, circumferential, and global longitudinal strain and strain rates were measured. Moreover, multilayer characterization of the left ventricle was assessed.

3D echocardiographic examination was performed from the apical view, during apnea, allowing volume acquisition from consecutive three separate multi-beat datasets of the left ventricle by combining six consecutive ECG-triggered sub-volumes to obtain high temporal resolution. A 12-slice display mode was selected to ensure that the entire cavity and walls of the left ventricle were included in the full volume. All data sets were digitally stored in a raw-data format and exported to work stations equipped with quantitative software, 4DAutoLVQ (EchoPAC GE Healthcare, version BT 13) and TomTec package. The measured parameters are listed in Table 2.

Statistical analysis. We evaluated normal distribution of parameters using Kolmogorov-Smirnov test. Continuous variables are presented as mean +/- standard deviation, and categorical variables as percentages. Comparison of continuous variables was performed using independent samples T-test, while the analysis of progression of continuous variables in time, differentiated between study subgroups, was performed using the Anova test for repeated measures. Comparison between categorical variables was made using Pearson Chi-Squared test. Inter-observer variability was assessed for 20 subjects randomly chosen, by two independent observers. One observer repeated the measurements of the same datasets to assess intra-observer variability. Reproducibility was reported as intra-class correlation coefficient (ICC). All analyses were carried out using IBM SPSS version 23.0. Differences among variables were considered significant at $p<0.05$. ❑

Parameters / Method	Left ventricular systolic function
2D echocardiography	➢ Ejection fraction (modified Simpson's)
3D echocardiography	➢ Ejection fraction (TomTec and 4DAutoLVQ) ➢ Global longitudinal strain
2D echocardiography – Tissue Doppler imaging	➢ S wave velocity at the lateral and medial mitral annulus
2D echocardiography – Speckle tracking	➢ Radial strain ➢ Circumferential strain ➢ Longitudinal strain ➢ Multi-layer analysis for longitudinal strain (endocardium, epicardium, and middle longitudinal strain)

TABLE 2. Echocardiographic parameters

RESULTS

Study population. We enrolled 87 women with a mean age of 32±4 years. All of them completed the four planned visits. Based on blood analysis results and personal and familial history of thrombosis, we divided the whole group into two subgroups: one with inherited thrombophilia (22 subjects) and the control group (65 subjects). Those belonging to the thrombophilia group received anticoagulant treatment with low weight molecular heparin for primary preven-

Parameter	Group 1 Thrombophilia group N = 22	Group 2 Control group N = 65	p-value
Age	32±5	33±4	0.363
Weight before pregnancy (kg)	60±9	63±11	0.305
Weight visit 1 (kg)	62±9	64±12	0.396
Weight visit 2 (kg)	68±9	69±12	0.597
Weight visit 3 (kg)	73±8	75±12	0.488
Weight visit 3 (kg)	61±9	64±11	0.372
Current smoker (%)	18	17	0.893
Primiparous (%)	96	97	0.564
***In vitro* fertilization (%)**	0	1.5	0.747
History of pregnancy loss during first semester (%)	19	12	0.612
History of pregnancy loss during second semester (%)	9	5	0.180
History of pregnancy loss during third semester (%)	0	0	0.747
History of prematurity (%)	0	3	0.556
History of gestational hypertension (%)	4.5	4.6	0.736

TABLE 3. Clinical characteristics of the study groups

sion, dosed according to current guidelines, beginning with 15±3 weeks of pregnancy (7, 10). There were no significant differences in age, height, systolic and diastolic blood pressure, personal medical history between groups. Heart rate, weight, and BSA of pregnant women increased during pregnancy, and recovered after pregnancy. The clinical characteristics of the study groups are presented in Table 3.

Left ventricular systolic function during pregnancy. There were no differences between groups for any of the echo parameters, at each of the four visits (Table 4). At visit 1, left ventricular ejection fraction had normal values, for both 2D and 3D echo assessment. At second and third visits, parameters of left ventricular systolic function had lower values for all subjects, with no differences between groups. Comparing the third visit with the first one, all parameters of left ventricular systolic function had significantly lower values at the end of pregnancy (third visit) (Table 5). Left ventricular systolic function decreased from 58% to 55% (2D modified Simpson's), from 60% to 56% (3D TomTec), and from 58% to 55% (Auto4DLVQ), with $p<0.001$ for all three methods.

Clinical impact of the inherited thrombophilia. During pregnancy, there were no thrombotic events among groups. Five subjects (5.7%) from the entire group presented one venous thrombotic event in their personal medical history and all of them were included in the inherited thrombophilia subgroup. Thus, high risk mutation correlated positively with the probability of spontaneous thrombotic events (Fisher Exact Test with $p=0.001$, Phi coefficient 0.424 with $p<0.001$). There were 12 cases of gestational hypertension which needed medication, eight of them from

Parameter \ Group	Group 1 Thrombophilia group N = 22	Group 2 Control group N = 65	p-value (between groups difference)
	Visit 1 (15±2 weeks of pregnancy)		
2D LVEF modified Simpson's (%)	57.6±2.9	57.7±3.1	0.957
3D LVEF – TomTec analysis (%)	60.3±2.7	60.3±3.1	0.967
3D LVEF – Auto4DLVQ (%)	57.3±2.4	58.5±4.5	0.553
TDI – Medial mitral annular S wave velocity (cm/s)	9.3±1.2	9.3±1.2	0.987
TDI – Lateral mitral annular S wave velocity (cm/s)	12.5±1.8	12.3±2.1	0.684
2D Speckle tracking – radial strain	21.7±4.7	23.9±6.7	0.081
2D Speckle tracking – radial strain rate	1.6±0.6	1.9±0.7	0.080
2D Speckle tracking – circumferential strain	19.8±2.8	20.6±4.3	0.400
2D Speckle tracking – circumferential strain rate	1.5±0.4	1.6±0.5	0.236
2D Speckle tracking – global longitudinal strain	18.6±2.8	19.1±2.4	0.361
2D Speckle tracking – longitudinal strain, epicardial layer	19.5±3.1	20.4±2.6	0.167
2D Speckle tracking – longitudinal strain, middle layer	18.6±2.1	19.2±2.4	0.319
2D Speckle tracking – longitudinal strain, endocardial layer	16.7±3.7	17.4±2.5	0.400
3D Global longitudinal strain	18.4±2.8	19.1±2.4	0.195
	Visit 2 (25±2 weeks of pregnancy)		
2D LVEF modified Simpson's (%)	55.9±2.1	56.5±2.1	0.530
3D LVEF – TomTec analysis (%)	57.2±1.8	57.1±1..8	0.822
3D LVEF – Auto4DLVQ (%)	55.9±1.4	56.1±2.3	0.681
TDI – Medial mitral annular S wave velocity (cm/s)	8.6±1.8	8.5±1.9	0.555
TDI – Lateral mitral annular S wave velocity (cm/s)	10.5±1.2	10.6±1	0.777
2D Speckle tracking – radial strain (%)	19.4±5.5	21.8±6	0.141
2D Speckle tracking – radial strain rate (%)	1.6±0.6	1.7±0.5	0.253
2D Speckle tracking – circumferential strain (%)	17.8±4.1	19.1±4	0.230
2D Speckle tracking – circumferential strain rate (%)	1.4±0.3	1.4±0.4	0.853
2D Speckle tracking – global longitudinal strain (%)	16.6±1.9	17.4±2.5	0.179
2D Speckle tracking – longitudinal strain, epicardial layer (%)	17.7±2.6	18.6±2.4	0.137

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2D Speckle tracking – longitudinal strain, middle layer (%)	17.5±2.6	18.1±2.3	0.343
2D Speckle tracking – longitudinal strain, endocardial layer (%)	15.3±2.6	16.4±2.6	0.054
3D Global longitudinal strain (%)	16.6±1.9	17.4±2.5	0.151
	Visit 3 (35±2 weeks of pregnancy)		
2D LVEF modified Simpson's (%)	55.4±1.9	56±1.8	0.210
3D LVEF – TomTec analysis (%)	55.7±1.4	56±1.6	0.240
3D LVEF – Auto4DLVQ (%)	54.7±1.2	55.3±1.9	0.120
TDI – Medial mitral annular S wave velocity (cm/s)	7.7±0.6	8±1	0.114
TDI – Lateral mitral annular S wave velocity (cm/s)	8.3±1.4	9±1.3	0.076
2D Speckle tracking – radial strain (%)	18.5±4.6	20.5±6	0.137
2D Speckle tracking – radial strain rate (%)	1.6±0.6	1.7±0.6	0.805
2D Speckle tracking – circumferential strain (%)	16.5±4.3	17.7±4.1	0.254
2D Speckle tracking – circumferential strain rate (%)	1.2±0.4	1.2±0.4	0.724
2D Speckle tracking – global longitudinal strain (%)	15.2±2.6	16.2±2.7	0.141
2D Speckle tracking – longitudinal strain, epicardial layer (%)	16.5±2.6	17.6±2.8	0.123
2D Speckle tracking – longitudinal strain, middle layer (%)	15.3±2.6	16.3±2.7	0.081
2D Speckle tracking – longitudinal strain, endocardial layer (%)	14.3±2.5	15.2±2.7	0.113
3D Global longitudinal strain (%)	15.1±2.3	16±2.1	0.098
	Visit 4 (35±2 weeks after giving birth)		
2D LVEF modified Simpson's (%)	56.2±2.4	56.9±2.6	0.242
3D LVEF – TomTec analysis (%)	60±2.6	60.4±3.1	0.648
3D LVEF – Auto4DLVQ (%)	57±3.7	57.9±4	0.514
TDI – Medial mitral annular S wave velocity (cm/s)	9±0.9	9.2±1.2	0.399
TDI – Lateral mitral annular S wave velocity (cm/s)	8.4±1.4	9±1.3	0.061
2D Speckle tracking – radial strain (%)	24.5±4.9	26.7±6.9	0.166
2D Speckle tracking – radial strain rate (%)	1.7±0.3	1.7±0.4	0.848
2D Speckle tracking – circumferential strain (%)	20.4±2.4	21.4±2.9	0.162
2D Speckle tracking – circumferential strain rate (%)	1.4±0.3	1.5±0.4	0.120
2D Speckle tracking – global longitudinal strain (%)	18±2.6	18.9±2.4	0.156
2D Speckle tracking – longitudinal strain, epicardial layer (%)	19.7±3.1	20.1±3.4	0.638
2D Speckle tracking – longitudinal strain, middle layer (%)	17.5±3.4	19±2.5	0.630
2D Speckle tracking – longitudinal strain, endocardial layer (%)	16.8±3.3	17±2.6	0.665
3D Global longitudinal strain (%)	18±1.7	19±2.7	0.075

LVEF = left ventricle ejection fraction; TDI = tissue Doppler imaging.

TABLE 4. Left ventricular systolic function during pregnancy

the control group and four from thrombophilia group. There were 29 cases of intrauterine growth restriction, 11 of them from mothers with high risk inherited thrombophilia. There was a positive correlation between the risc of inherited thrombophilia and intrauterine growth restriction ($r=0.224$, $p=0.037$).

Reproducibility. In 3D echocardiography, inter- and intra- observer variability for the left and right ventricular ejection fractions had good intra-class correlation coefficients. For inter-observer variability, ICC was 0.855 for the left ventricular ejection fraction (Auto4DLVQ) and 0.799 for the right ventricular ejection fraction ($p<0.001$ for both), while for intra-observer variability ICC was 0.946 for the left ventricular ejection fraction (Auto4DLVQ) and 0.930 for the right ventricular ejection fraction ($p<0.05$ for both).

Comments

For the cardiovascular system, pregnancy is equivalent to a prolonged effort test. Therefore, in normal pregnancy preload increases, afterload

	Mean difference between visit 1 and visit 3	p-value for trend
2D Speckle tracking – radial strain (%)	-3.3±5.2	<0.001
2D Speckle tracking – radial strain rate (%)	- 0.9±0.7	0.024
2D Speckle tracking – circumferential strain (%)	- 3.2±4.6	<0.001
2D Speckle tracking – circumferential strain rate (%)	- 0.4±0.5	<0.001
2D Speckle tracking – global longitudinal strain (%)	- 3.0±2.2	<0.001
TDI – Medial mitral annular S wave velocity (cm/s)	- 0.5±0.7	<0.001
TDI – Lateral mitral annular S wave velocity (cm/s)	- 3.5±1.5	<0.001

TABLE 5. Left ventricular systolic function during pregnancy

decreases, and left ventricular remodeling occurs. All of these determine mild dilation of the left ventricle. Concomitantly, ventricular mass increases by higher vascular endothelial growth factor expression, which causes myocardial angiogenesis without parallel fibrosis development (11, 12). Thus, there is a reversible eccentric hypertrophy. While the hemodynamic changes occurring during pregnancy have been clearly described, the impact of pregnancy on cardiac contractile function has not been fully elucidated.

The current study does a comprehensive analysis of the cardiac systolic function using all the current available echocardiographic parameters in a group of pregnant women who were genetically tested for inherited thrombophilia. To the best of our knowledge, this is the first study evaluating cardiac systolic function in pregnant women tested for inherited thrombophilia.

Each women included in our study had at least one mutation confirmed by genetically blood analysis. We defined two subgroups, based on the risk of developing thrombotic events, risk given by the type of genetic defect, number of mutations and personal/familial history of thrombotic efects. Thrombophilic subjects had one of the following: personal history of a thrombotic event and any type of inherited thrombophilia or homozygous mutation or double heterozygous mutation for factor V Leyden, prothrombin G20210A or antithrombin III genes. They received prophylactic anticoagulant therapy with Enoxaparin 0.4 mg/day. The rest of the subjects (making the control group) had one heterozygous mutation for factor V Leyden, MTHFR, factor III or prothrombin genes, protein C or protein S deficiencies or PAI (Plasminigen Activator Inhibitor) polymorphism; these mutations are not related with increased hypercoagulability, and do not need prophylactic anticoagulant treatment during pregnancy (6, 7, 10, 13, 14).

Left ventricular systolic function. Our data about left ventricular systolic function during pregnancy is concordanct with the previous studies. Thus, left ventricular systolic function (by 2D and 3D echocardiography) had normal values, with a mild decrease during pregnancy and no significant differences between groups (5, 15, 16). Similarly, parameters measured by speckle tracking and tissue Doppler had the same trend as the left ventricular ejection fraction, with a mild decrease during pregnancy and complete recovery at six months after giving birth, comparable with other papers in normal pregnancy (5, 16).

Pregnancy outcomes related with inherited thrombophilia. There are many data demonstrating a relation between fetal growth restriction, pregnancy loss (early and late), and inherited thrombophilia, the pathogenic mechanism being the presence of thrombosis in the placental vascularization (18). Data from our study have also showed a weak but significant correlation between the presence of growth restriction at birth and inherited thrombophilia ($r=0.224$, $p=0.037$). In our study population, all thrombotic events were observed in the group with inherited thrombophilia. In fact, there was a significant correlation between the probability of spontaneous thrombosis and the risk of thrombotic events given by the type of mutation (Fisher Exact Test with $p=0.001$, Phi coefficient 0.424, with $p<0.001$).

Limitations. The current monocentric study had a small number of patients. From ethical considerations, subjects with inherited thrombophilia were evaluated under anticoagulant treatment. However, it is unlikely that the anticoagulation treatment modifies the parameters of cardiac function in any way. ❑

CONCLUSION

Cardiac contractility has a slight, progressive decrease during pregnancy, which recovers completely at six months after giving birth. Thrombophilic mutation has no impact on the left ventricular systolic function. ❑

Conflicts of interest: none declared.
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