Pregnancy-related changes in Doppler gradients and left ventricular mechanics in women with subvalvular or valvular aortic stenosis.

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Abstract

Background: The aim of our study was to characterize echocardiographic changes during pregnancy in women with known LVOT obstruction or AS compared to the healthy pregnancy controls, and to assess the relationship with pregnancy outcomes. Methods: We retrospectively studied 34 pregnant patients with congenital LVOT obstruction or AS with healthy age-matched pregnant controls. Patients with other significant valvular lesions, structural heart disease (LVEF <40%), or prior valve surgery were excluded. All LVOTO/AS patients underwent a minimum of 2 consecutive echocardiograms between 1 year pre-conception up to 1 year postpartum, with at least 2 studies during the pregnancy. Comprehensive echocardiographic evaluation was performed including speckle-tracking LV global longitudinal strain. Results: A total of 83 echocardiograms from the study group and 34 echocardiograms from the control group were evaluated. Over the range of LVOTO/AS, a significantly greater increase in the AV gradients and LV and LA volumes were observed as compared with the controls. In the sub-group of LVOTO/AS pregnant women with > moderate (n=8) vs.

Pregnancy related changes in Doppler gradients and left ventricular mechanics in women with subvalvular or valvular aortic stenosis.

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ABSTRACT

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Results: A total of 83 echocardiograms from the study group and 34 echocardiograms from the control group were evaluated. Over the range of LVOTO/AS, a significantly greater increase in the AV gradients and LV and LA volumes were observed as compared with the controls. In the sub-group of LVOTO/AS pregnant women with > moderate (n=8) vs. <moderate LVOTO/AS (n=26), averaged $2^{nd}/3^{rd}$ trimester LVEF was lower (51(12)% vs. 58(4)%, p=0.02) and GLS was lower (-19.5(2.8) vs. -21.2(2.4), p=0.06). Pregnancy was well tolerated despite these changes.

Conclusion: Among pregnant women with even milder forms of LVOTO/AS, increases in cardiac volumes and AV gradients can be expected over the course of pregnancy. Significant decreases in LV function and mechanics were only observed in women with moderate or greater LVOTO/AS, although still remained in normal range.

Keywords: Speckle tracking echocardiography, global longitudinal strain, left ventricular outflow tract obstruction, aortic stenosis, pregnancy.

Abbreviations

2D-STE = Two-dimensional speckle tracking echocardiography

AS = Aortic stenosis

AR = Aortic regurgitation

AVA = Aortic valve area

BSA = Body surface area

BMI = Body mass index

CHD = Congenital heart defect

CO = Cardiac output

CoA = coarctation of the aorta

GA = Gestational age

GLS = Global longitudinal strain

LV = Left ventricular

LVEF = Left ventricular ejection fraction

LVOT = Left ventricular outflow tract

LVOTO/AS = Left ventricular outflow tract obstruction

SV = Stroke volume

INTRODUCTION

Left ventricular outflow tract obstruction (LVOTO/AS) malformations account for approximately 14% of all congenital heart disease (CHD)[1,2]. Types of lesions include subaortic membrane, bicuspid aortic valve, and supravalvular aortic stenosis. These may occur individually or in association with other anomalies such as coarctation of aorta or hypoplastic left heart[3]. All lesions result in varying degrees of systolic flow obstruction from the left ventricle (LV) to the ascending aorta[4].

Pregnancy is a state of increased physiologic demand and profound hemodynamic changes which results in increased preload and cardiac output[5–7]. As such, valvular Doppler gradients are expected to increase with normal pregnancy. While women with LVOTO/AS are routinely assessed with echocardiography throughout preconception and pregnancy, there is a paucity of knowledge regarding the impact of pregnancy on LVOTO/AS and what can be considered a physiological vs. pathological change[8–10]. Furthermore, this has not been studied in conjunction with sub-clinical changes in left ventricular function measured by global longitudinal strain (GLS), which has emerged as an important measure of subclinical left ventricular dysfunction with a prognostic role in patients with cardiac disease[11–14]. In particular, among patients with moderate AS or asymptomatic severe AS and preserved LVEF, impaired left ventricular GLS has been shown to be associated with increased risk for progression and a marker for earlier intervention[15–18].

The objectives of this study were to determine among women with congenital LVOTO/AS: 1) changes in LVOT Doppler gradients over the course of pregnancy and postpartum as compared to controls; 2) changes in left ventricular function evaluated by left ventricular ejection fraction (LVEF) and GLS over the course of pregnancy and postpartum as compared to controls; and 3) if there is an association between LVOT Doppler gradients and left ventricular function with clinical outcomes.

MATERIALS AND METHODS

Study Population

A single-center retrospective study was conducted using the Cardiology Obstetrics (COB) database at St. Paul's Hospital (Vancouver, Canada). Consecutive, retrospective pregnancies were identified with established diagnosis of congenital LVOTO/AS (bicuspid aortic valve; bicuspid aortic valve/aortic coarctation; sub-valvular aortic stenosis; and bicuspid aortic valve/sub-valvular stenosis) who underwent singleton pregnancy between February 2008 and December 2020. In order to be included, each pregnant woman had to have at least 2 comprehensive transthoracic echocardiograms (TTE) during index pregnancy, each performed during a different trimester. Exclusion criteria included: (1) previous valve surgery; (2) other moderate or severe heart valve disease; (3) cardiomyopathy with LVEF < 40%; (4) persistent arrhythmias; (5) pregnancy terminated at < 20 weeks gestation; (6) age less than 18 years; (7) presence of other medical comorbidities; and (8) poor image quality such that comprehensive echocardiographic assessment of left ventricular function and semi-automated GLS analysis could not be performed. For the control group, healthy age-matched women with a singleton pregnancy who were referred to the COB clinic with comprehensive echocardiography at the time of referral but found to have no evidence of significant cardiac disease were enrolled. All patients provided written consent and approval was obtained from the University of British Columbia's Research Ethics Board.

Data Collection

Baseline clinical data for cases and controls were obtained through electronic chart review. For all women, the following data were recorded: maternal age, parity, pre-pregnancy height and weight, baseline pre-pregnancy or early pregnancy vital signs (blood pressure, heart rate), anatomic details of cardiovascular disease (study group), cardiac surgical/interventional history, baseline New York Heart Association functional class and medication history. When available, obstetric and labour/delivery information was also collected.

Outcomes

Adverse events during the ante-, peri-, and postpartum periods were classified as maternal cardiac, obstetrical, and fetal/neonatal. Two physicians (JG, AC) blinded to the women's baseline characteristics independently verified adverse events. Adverse cardiac events were defined as any of the following: left sided heart failure (HF) defined as pulmonary edema documented by chest radiograph or crackles heard over at least one third of posterior lung fields and jugular venous distension, right-sided HF, sustained atrial or ventricular tachyarrhythmias requiring treatment, stroke or transient ischemic attack, cardiac thromboembolism, myocardial infarction, cardiac arrest, or cardiac death. Obstetrical outcomes were defined as gestational hypertension, pre-eclampsia or eclampsia, hemorrhage, and premature rupture of membranes. Fetal and neonatal complications were defined as miscarriages, premature birth ($<$37 weeks gestation), small-for-gestational-age birth weight ($<$10th percentile for gestational age and sex or $<$ 2500 g), neonatal ICU admission, fetal death (after 20 weeks gestation and before birth), or neonatal death (from birth to age 28 days).

Echocardiographic Examination

Comprehensive transthoracic echocardiography was performed using Philips IE 33 system (Philips Medical Systems, Bothell, WA, USA). Images were stored and analyzed using Syngo software platform (Siemens Medical Solutions, MI, US). Standard echocardiographic parameters of left atrial volume; LV size and systolic and diastolic function; LVOT and aortic valve (AV) gradients and AV area were measured by the primary reader (AC) under the guidance of an experienced echocardiographer (JG) according to the recommendations of American Society of Echocardiography (ASE) guidelines[13,14].

For left ventricular global longitudinal strain analysis (GLS), Tomtec Cardiac Performance Analysis version 1.3.0.91 was used (Unterschliessheim, Germany). The software detects lateral and septal walls and divides each into three segments (basal, mid, and apical) to calculate the strain via speckle tracing. An average strain for entire LV in apical four chamber, apical two chamber, and apical three chamber views were used to calculate the GLS. Strain measurement was accepted after visual inspection and when the software demonstrated adequate tracking. If tracking was suboptimal, the endocardial border was manually retraced. Ten subjects were randomly selected to calculate the interobserver variability between the measurements of two independent investigators (AC, JG). Both investigators were blinded to each result.

Statistical Analysis

Mean $\pm$ standard deviation and numbers (percentages) summarized continuous and categorical variables, respectively, for baseline characteristics measurements. Mean $\pm$ standard deviation are presented for echocardiographic parameters through pregnancy. Echocardiographic parameters averaged for the 2nd/3^{rd}trimester values were compared for cases vs. controls with one way ANOVA analysis. Overall trend of echocardiographic parameters over the course of pregnancy was determined by mixed effects regression analysis for the cases.

RESULTS

Baseline characteristics:

During the study period, 117 patients with diagnosis of native LVOTO/AS were seen in the Cardiac Obstetrics Clinic. A total of 34 pregnancies fulfilled our study criteria. A majority of patients were excluded due to the lack of serial TTE studies (n=64). Other reasons for exclusion were presence of other cardiac and medical comorbidities (n=49) or early termination of pregnancy $<$ 20 weeks (n=4). The patient baseline characteristics are summarized in Table 1. The cases had the following diagnoses: bicuspid aortic valve (18, 53%); bicuspid aortic valve/aortic coarctation (14, 41%); sub-valvular aortic stenosis (1, 3%) and bicuspid aortic valve/sub-valvular stenosis (1, 3%).

All of the controls were NYHA I at the time of pregnancy. The control group had the following referral diagnoses: murmur (9, 26%); presyncope (4, 12%); palpitations (14, 41%); electrocardiogram abnormalities

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(2, 6%); screening due to family history (5, 15%). The case/control groups were similar in age, pre-or early pregnancy blood pressure/heart rate and BMI.

Echocardiographic characteristics:

The echocardiographic changes in the LVOTO/AS group over the course of pregnancy and post-partum are shown in Table 2. In the LVOTO/AS group, there was an overall increase in the aortic valve peak gradient from preconception to the 3rd trimester (Table 3 and Figure 1). The left ventricular and left atrial size increased and left ventricular ejection fraction decreased overall from preconception to the 3rd trimester (Table 3 and Figure 1). The left ventricular GLS, however, increased over this time.

The averaged 2nd/3rd trimester left ventricular dimension, left ventricular volume, cardiac output and aortic valve peak gradient were significantly increased in the pregnant LVOTO/AS group as compared to pregnant controls (Table 2). LVEF, left ventricular diastolic parameters and left ventricular global longitudinal strain were similar to between LVOTO/AS and control groups. However, in the sub-group of LVOTO/AS pregnant women with> moderate (n=8) vs. < moderate LVOTO/AS (n=26), averaged 2nd/3rd trimester LVEF was lower (51 +- 12% vs. 58 +- 4%, p=0.02) and GLS was lower (-19.5 +- 2.8 vs. -21.2 +- 2.4, p=0.05).

Adverse Maternal and Fetal/Neonatal Outcomes:

All women in both LVOTO/AS and control groups were asymptomatic at baseline. There were no adverse maternal cardiac outcomes in the LVOTO/AS group (Table 4). Two women in the control group had supraventricular tachycardia during 2nd trimester of their pregnancy (Table 4). Obstetrical outcomes were similar between the two groups, although a trend to increased rate of gestational hypertension, miscarriage, and pre-term deliveries were observed. Three adverse fetal events occurred in the LVOTO/AS group and none in the control group (Table 4).

DISCUSSION

In the current study, we aimed to characterize gestational changes in LVOTO/AS Doppler gradients and LV mechanics in women with LVOTO/AS as compared to pregnant controls and to assess the relationship with pregnancy outcomes. In our cohort of asymptomatic women with overall moderate LVOTO/AS, we found that AV peak gradient, left ventricular size and left atrial size increased over the course of pregnancy compared to controls. Although left ventricular function and mechanics were preserved in this cohort, there were dynamic changes over pregnancy with a trend to declining LVEF and small increase in GLS over the course of pregnancy. We also found that in this cohort of women with a range of LVOTO/AS, left ventricular size parameters, CO, and AV gradients were significantly increased as compared to controls. Although there was no overall significant difference in left ventricular function and mechanics between all LVOTO/AS cases and controls, there was certainly a lower LVEF and GLS among those with moderate or greater LVOTO/AS as compared to controls. Pregnancy was well tolerated in all women with LVOTO/AS in this study with no deterioration in functional status or cardiac decompensation.

Studies focusing on sequential changes in LV function and mechanics over the course of normal pregnancies have been limited but would suggest no significant change occurs. Several older studies have shown that LVEF by 2D echocardiography remained stable during a normal pregnancy[21–24]. One study of a healthy pregnant cohort using 3D echocardiography observed a slight reduction in LVEF in late pregnancy with return to baseline at postpartum[25]. In another study of 36 healthy women, Sengupta and colleagues showed that global longitudinal and circumferential strain decreased while the radial strain increased during pregnancy, and postulated that these counterbalancing changes served to maintain the overall LVEF[26]. To our knowledge, only 2 studies have evaluated gestational changes in AV Doppler gradient and LV function and mechanics in women with LVOTO/AS. In a study of 6 women with congenital AS, Samiei et al reported an increase in the AV peak gradient from first trimester to third trimester (30.8 +- 12.1 to 38 +- 19.5)[9]. Left ventricular function was not evaluated in this study. In a separate study, Tzemos et al. assessed 10 women with at least moderate congenital AS, and found that AV peak gradient rose from 59 +- 7 mmHg (prepartum) to 70 +- 9 mmHg (antepartum)[8]. This group also assessed left ventricular mechanics, and found that LVEF and left

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ventricular longitudinal strain remained unchanged.

Our larger case control study similarly shows that AV gradients and LV and LA volumes increase over the course of pregnancy and significantly more in the LVOTO/AS cases as compared to pregnant controls. This is an important observation as clinicians should expect that gradients and cardiac volumes will increase across the spectrum of LVOTO/AS severity and to a greater degree than seen in pregnancies without structural heart disease. It is important to note that our cohort consisted of mostly mild LVOTO/AS (26/34, 76%). Left ventricular function and mechanics remained in the normal range over the course of LVOTO/AS pregnancies, although LVEF trended to decline even in this cohort with milder forms of LVOTO/AS.

Numerous studies outside of pregnancy have demonstrated that increasing LVOTO/AS and the consequent LVH leads to impaired compliance, high filling pressures, and eventual replacement of interstitial space with reactive fibrosis[27–31]. In patients with AS, left ventricular GLS has been shown to detect this adverse remodeling before LVEF declines, and further deteriorates over time[15,16,18,27]. These changes certainly can complicate the hemodynamic adaptations required for an event free pregnancy.

Pregnancy with pre-existing significant left heart obstruction has been shown to be associated with increased risk of maternal cardiac events, as well as adverse obstetrical and fetal/neonatal outcomes[32]. Presence of a fixed obstruction and the reduced ability to augment stroke volume in setting of an increased physiologic demand of pregnancy is believed to be the mechanism for decompensation in women with LVOTO/AS[10,26,33]. Despite changes in cardiac size and trends to a declining LVEF, there were no adverse cardiac events in our study's LVOTO/AS group. This is likely due to the fact that LV function and mechanics remained in the normal range over the course of pregnancy for this entire cohort with mostly mild LVOTO/AS. An important observation is that LV function and mechanics were significantly lower in the moderate or greater LVOTO/AS group as compared to milder LVOTO/AS although still in the normal range. This would suggest that changes in function and mechanics likely play a role in cardiac decompensation in cases of significant LVOTO/AS with clinically relevant decline in LV function and mechanics. There was a trend to increased rate of gestational hypertension which has been previously documented among women with aortic coarctation. Finally, more miscarriage and preterm deliveries occurred in the study group, both of which are common fetal/neonatal complication encountered among woman with structural heart disease.

Study limitations:

This was a retrospective study, and therefore there was considerable variation in the timing of echocardiographic studies. However clinical practice would dictate timing to coincide with trimester. At our centre, it is a routine practice to obtain a baseline echocardiogram at the time of the referral and also a repeat echocardiogram during 2nd trimester in women with LVOTO/AS. This likely mitigates some of the issues surrounding potential selection bias. Secondly, our study had a very small number of women with moderate or greater LVOTO/AS. This may potentially explain why the event rates for obstetrical and fetal/neonatal outcomes were also low. Finally, we assessed only the longitudinal strain, without measuring the circumferential or the radial strain. However, we feel that the longitudinal strain is the most clinically relevant marker, and the other types of strain are less applicable in clinical practice.

CONCLUSION

Among pregnant women with even milder forms of LVOTO/AS, increases in cardiac volumes and AV gradients can be expected over the course of pregnancy and to a greater degree than in pregnant women without structural heart disease. Despite this, LV function and mechanics remain in the normal range with LV function showing a trend to decline over the course of pregnancy. No adverse cardiac events were observed in this cohort. Significant LVOTO/AS is associated with reduced LV function and mechanics as compared to mild LVOTO/AS, and in the event of clinically relevant reduction, would likely account for adverse events. This warrants further study with a focus on sequential LV function/mechanics assessment over the course of pregnancy among those with only significant LVOTO/AS.

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AUTHOR CONTRIBUTIONS

SAC contributed to the study protocol, data collection and interpretation, and drafting of the manuscript. JG contributed to the overall study concept/design, statistical analysis, and the manuscript. PK and MJ contributed to the data collection. MK and VR reviewed the manuscript for critical revision.

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FIGURE 1. Echocardiographic changes over the course of pregnancy in women with LVOTO/AS and the overall regression line (red line). Each line represents an individual LVOTO/AS case, with dots representing each visit. Time points #1= pre-pregnancy #2=1st trimester #3=2nd trimester #4=3rd trimester

TABLES

Table 1. Baseline characteristics

Variable	Control group (n = 34)	LVOTO/AS group (n
Age (years)	30.5+4.9	30.6+4.8
Systolic blood pressure (mmHg	113.2+8.6	112.5+12.6
Diastolic blood pressure (mmHg)	63.9+7.1	67.7+10.5
Body surface area (kg/m^2)	1.8+0.1	1.8+0.1
Body mass index (m^2)	25.0+3.1	26.2+4.8
Cardiac medications Beta blocker Calcium channel blocker	11 (32%) 1 (3%)	5 (15%) 0 (0%)

Data are expressed as n (%) or mean $\pm$ SD

Table 2. Echocardiographic changes during pregnancy in women with LVOTO/AS and controls*

Variable	Pre-Pregnancy	1st Trimester	2nd Trimester	3rd Trimester	Post-Partum	Avg LVOTO/AS	Avg controls	p^
Heart rate, bpm	71 (11)	69 (11)	73 (12)	77 (15)	62 (7)	77 (14)	78 (15)	0.78
LVEDD, mm	45 (3)	47 (5)	49 (6)	50 (6)	45 (16)	49 (6)	45 (5)	**0.02**
LVEDV, ml	131 (11)	134 (31)	137 (26)	141 (23)	129 (36)	138 (26)	126 (26)	0.88
LVESV, ml	55 (11)	53 (16)	58 (14)	63 (15)	55 (11)	60 (14)	52 (12)	**0.03**
LVEF, %	59 (7)	61 (6)	57 (8)	56 (6)	59 (6)	56 (7)	57 (11)	0.81
CO, l/min	4.8 (2.0)	5.6 (1.7)	6.2 (5.5)	5.9 (1.7)	4.5 (1.7)	5.7 (1.6)	4.2 (1.5)	**0.001**
LAV, ml	43 (9)	47 (7)	53 (13)	55 (12)	53 (13)	54 (12)	53 (15)	0.86
Mitral E/a	1.5 (0.4)	1.9 (0.8)	1.7 (0.5)	1.5 (0.4)	1.8 (0.4)	1.7 (0.5)	1.7 (0.6)	0.96
E' medial	10.3 (1.5)	9.2 (1.7)	10.2 (2.6)	9.5 (2.4)	9.0 (2.1)	10.1 (2.7)	10.7 (2.7)	0.45

Variable	Pre-Pregnancy	1st Trimester	2nd Trimester	3rd Trimester	Post-Partum	Avg LVOTO/AS	Avg controls	p^
E' lateral	13.4 (3.6)	13.7 (4.1)	15.0 (3.4)	13.0 (2.9)	12.8 (3.0)	14.5 (3.2)	14.3 (4.7)	0.89
LVOT PW	5.1 (1.4)	3.8 (1.7)	6.6 (9.4)	7.4 (9.8)	4.1 (1.3)	8.0 (10.8)	4.6 (1.7)	0.14
AV PG	21.3 (14.7)	23.5 (14.1)	28.0 (19.8)	26.0 (17.4)	22.4 (17.1)	27.4 (19.8)	9.0 (2.7)	**<0.001**
GLS	-22.1 (1.8)	-22.5 (2.2)	-21.0 (2.5)	-19.7 (3.1)	-21.9 (2.4)	-20.8 (2.6)	-21.8 (1.8)	0.10

* mean (SD), ^ LVOTO/AS cases vs. control (comparison of average of 2nd/3rd trimester)

Table 3. Echocardiographic changes in LVOTO/AS cases over pregnancy

	Estimate (95% CI)	P
HR	2.13 (-0.19, 4.44)	0.07
LVEDD	0.62 (-0.09, 1.32)	0.08
LVEDV	2.12 (-2.19, 6.43)	0.32
LVEF	-1.59 (-3.28, 0.10)	0.06
CO	1.14 (-2.41, 4.68)	0.52
LA_vol	3.07 (0.60, 5.53)	**0.02**
Mitral_E_A	-0.04 (-0.15, 0.08)	0.52
TDI__medial_e	-0.21 (-0.70, 0.29)	0.39
TDI_lateral_e	-0.32 (-1.04, 0.40)	0.37
LVOT_peak_gradient	0.35 (-0.10, 0.80)	0.12
AV_peak_gradient	2.11 (0.31, 3.91)	**0.02**
LV_GLS	0.68 (0.15, 1.21)	**0.01**

Table 4. Maternal and Fetal/Neonatal Outcomes

Variable	Control group n = 34 (%)	LVOTO/AS group n = 34 (%)	P
Gestational age at delivery (years)	39	37.7	0.73
Birth weight (g)	3373.0	3363.7	0.48
Mode of delivery: (%) Spontaneous delivery Elective C-section Emergency C-section Forceps / vacuum assisted	12 (35.3) 5 (14.7) 6 (17.6) 5 (14.7)	14 (41.2) 10 (29.4) 3 (8.8) 5 (14.7)	0.80 0.24 0.47 -
Any adverse maternal events: Heart failure Arrythmia Hospitalization due cardiac cause Pre-eclampsia Deaths due to any cause	2 (5.9) 0 2 (5.9) 0 0 0	0 0 0 0 0 0	0.47

Variable	Control group n = 34 (%)	LVOTO/AS group n = 34 (%)	P
Any obstetrical complications: Gestational diabetes Gestational hypertension Pre-eclampsia Hemorrhage Premature rupture of membranes Other N/A	11 (32.4) 4 (11.8) 1 (2.9) 1 (2.9) 0 0 1 (chorioamnionitis) 4	9 (26.5) 1 (2.9) 4 (11.8) 0 1 (2.9) 0 0 3	0.79
Any fetal/neontal complications Miscarriage Preterm delivery (<37 weeks) Small for gestational age (<10th percentile for weight) Neonatal ICU admission N/A	5 (14.7) 0 0 0 0 5	5 (14.7) 1 (2.9) 2 (5.9) 0 0 2	-

Data reported as n (%) for categorical variables

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`Figure 1.pptx` available at https://authorea.com/users/420691/articles/526973-pregnancy-related-changes-in-doppler-gradients-and-left-ventricular-mechanics-in-women-with-subvalvular-or-valvular-aortic-stenosis