Doppler gradients, valve area and ventricular function in pregnant women with aortic or pulmonary valve disease: left versus right

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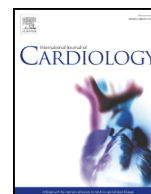# Doppler gradients, valve area and ventricular function in pregnant women with aortic or pulmonary valve disease: Left versus right

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ABSTRACT

Objective: Little is known about the course of echocardiographic parameters used for the evaluation of valvular heart disease (VHD) during pregnancy, hampering interpretation of possible changes (physiological vs. patho-physiological). Therefore we studied the course of these parameters and ventricular function in pregnant women with aortic and pulmonary VHD.
Methods: The cohort comprised 66 pregnant women enrolled in the prospective ZAHARA studies or evaluated by an identical protocol who had pulmonary VHD or aortic VHD (stenosis/prosthetic valve). The control group comprised 46 healthy pregnant women. Echocardiography was performed preconception, during pregnancy and 1 year postpartum. Peak gradient, mean gradient, aortic valve area (AVA)/effective orifice area (EOA), left ventricular ejection fraction (LVEF) and right ventricular function (RVF; TAPSE) were assessed.
Results: Peak and mean gradients increased during pregnancy compared to preconception in women with aortic VHD and controls ($p < 0.0125$), but not in women with pulmonary VHD. AVA/EOA remained unchanged. Preconception and postpartum gradients were comparable in all groups. Mean LVEF was normal in pregnant women with VHD and controls. Mean TAPSE was lower ($p < 0.001$) in women with pulmonary VHD compared to women with aortic VHD and controls (<20 mm vs. ≥23 mm; $p < 0.001$). In women with pulmonary VHD a decrease of TAPSE was observed during pregnancy ($p = 0.005$).
Conclusion: Physiological changes during pregnancy lead to increased Doppler gradients in women with aortic VHD. This increase was not found in women with pulmonary VHD, probably caused by impaired RVF. Therefore, evaluation of RVF during pregnancy might be important to prevent underestimation of the degree of stenosis.

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1. Introduction

Women with valvular heart disease (VHD) have an increased risk of maternal and fetal complications during pregnancy. This requires careful evaluation and management during pregnancy, including regular echocardiographic assessment [1,2]. However, little is known about

the (normal) course of Doppler gradients and valve area during pregnancy, hampering the interpretation of possible changes (physiological vs. pathophysiological). During pregnancy, cardiac output increases by approximately 50% (stroke volume augmentation and increased heart rate) and the intravascular volume increases (causing hemodilution) [3]. These physiological changes may lead to increased valvular Doppler gradients. Furthermore, pregnancy in women with (valvular) heart disease may result in deterioration of ventricular function that may cause underestimation of Doppler gradients [2,4,5]. A recent study showed that Doppler gradients of women with left-sided VHD increased during

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pregnancy. However the investigators did not measure Doppler gradients before and after pregnancy. In addition, the influence of ventricular function on these parameters was not assessed [6]. Moreover, there are virtually no data on right-sided valvular gradients. Therefore, we aimed to study the course of Doppler gradients, valve area and ventricular function during pregnancy (including pre-pregnancy and postpartum evaluation) in women with left- or right-sided lesions.

2. Methods

2.1. Study design and patient selection

This cohort study comprised pregnant women and healthy pregnant controls who were enrolled in the ZAHARA II and III study (2008–2015) or evaluated by an identical protocol. The ZAHARA studies are prospective multicenter observational cohort studies and observed pregnant women with congenital heart disease (CHD) according to identical protocols [7,8]. Women aged ≥18 years, with pulmonary stenosis (PS), a prosthetic pulmonary valve (PPV), aortic stenosis (AS), or a prosthetic aortic valve (PAV) and a pregnancy duration of ≤20 weeks were eligible for enrollment in the current study. In addition, echocardiographic evaluation ≤ one year preconception, during second and third trimester of pregnancy and ≤one year postpartum had to be performed. Echocardiograms ≥ one year preconception were accepted when peak and mean gradient where comparable with available first trimester measurements. Echocardiograms <3 months or >1 year postpartum were accepted when peak and mean gradient were comparable with preconception measurements. All the participating centers received approval of the medical ethics committee and all women (prospectively enrolled) provided written informed consent. The healthy controls were recruited from low risk midwife practices in Groningen and Rotterdam [7]. For the healthy controls, postpartum echocardiograms were also used as baseline measurements.

2.2. Pre-pregnancy characteristics and follow up

Preconception baseline data were extracted from the medical records at the first ante-partum visit. Baseline data included underlying heart disease, cardiovascular history, obstetric history, maternal age, cardiac status preconception (including New York Heart Association (NYHA) functional class), modified WHO risk class according to the ESC guidelines for maternal risk of cardiovascular complications [9], ECG, laboratory results and echocardiographic recordings, medication use and intoxications. Evaluation during pregnancy was performed at 20 and 32 weeks gestation and one year postpartum according to ZAHARA II protocol [7]. All echocardiograms were performed according to valvular heart disease specific protocols, evaluated offline and checked for consistency and accuracy by 2 experienced cardiac sonographers (A.S.S. and J.J.J.A.). Assessment of systolic function, chamber quantification and valvular function were performed according to current guidelines [10–12]. Left ventricular dysfunction was defined as ejection fraction (LVEF) <45% and right ventricular dysfunction as tricuspid annular plane systolic excursion (TAPSE) <17 mm.

Cardiovascular complications were evaluated during pregnancy and up to 6 months post-partum. Primary cardiovascular complications were defined as need for an urgent invasive cardiovascular procedure, heart failure (according to the guidelines of the European Society of Cardiology and documented by the attending physician [13]), new onset or symptomatic tachy- or bradyarrhythmia requiring new or extended treatment, thromboembolic events, myocardial infarction, cardiac arrest, cardiac death, endocarditis and aortic dissection. Neonatal complications were considered intra-uterine (≥20 weeks gestation), neonatal and infant death (≤1 year after birth), admission to the NICU, intraventricular hemorrhage (grade III–IV), neonatal respiratory distress syndrome, preterm birth (<37 weeks gestation), presence of CHD in the fetus, small for gestational age (birth weight < 10th percentile) and low birth weight (<2500 g).

2.3. Statistical analysis

Continuous variables with normal distribution are presented as mean with standard deviation ($\pm$SD), non-normally distributed variables as median with interquartile ranges, dichotomous variables as absolute numbers with percentages. Longitudinal comparison of continuous variables within groups at two time points was performed by using the paired t-test (normally distributed) or Wilcoxon signed rank test (not normally distributed). The groups of interest are: women with AS, women with PAV, women with PS, women with PPV and controls. The time points of interest for longitudinal comparison within groups are: preconception versus 2nd trimester, 2nd trimester versus 3rd trimester, 3rd trimester versus postpartum, preconception versus postpartum. For longitudinal comparison only patients with complete data available at the four time points were included. For correction for multiple testing, Bonferroni post hoc test was used ($p < 0.0125$). Comparison of continuous variables between groups was performed with the Student t-test or Mann-Whitney U test, depending on distribution. For the comparison of dichotomous variables, we used the χ^2 test or Fisher exact test, as appropriate. Statistical analyses were performed using SPSS V.23.0 (SPSS, Chicago, USA).

3. Results

3.1. Baseline characteristics

A total of 66 pregnant women with VHD were included. As controls, 46 healthy pregnant women were evaluated. Preconception characteristics are shown in Table 1. No significant differences were found in age at conception and BMI between the groups. The group of women with a PAV consisted of 5 women with a mechanical valve and 5 women with a bioprosthetic valve with a mean valve size of 21 [21 −23] mm and became pregnant 9 ± 7 years after surgery. The group of women with a PPV consisted of 1 woman with a mechanical valve and 20 women with a bioprosthetic valve. Mean valve size was 23 [22–25] mm. The interval between surgery and pregnancy was 13 ± 8 years after surgery. A peak gradient of the aortic valve ≥36 mmHg was present in 27% of the women with AS and in 40% of the women with a PAV. A baseline peak gradient of the pulmonary valve ≥36 mmHg was present in 31% of the women with PS. One woman with AS and one woman with a PPV had severe regurgitation of the aortic valve. Severe regurgitation of the pulmonary valve was also present in 3 women with PS and 3 women with a PPV. All women had NYHA class I or II at preconception and all VHD women were classified according to maternal risk in modified WHO class II or III, except one woman with PS (WHO class I).

3.2. Hemodynamic changes of the valves during pregnancy

The echocardiographic examinations were performed at 25.5 [13–52] weeks preconception, during pregnancy at 20.4 ± 2.2 and 31.7 ± 1.6 weeks respectively, and at 52 [37–57] weeks postpartum. Complete valve measurements throughout pregnancy of the aortic valve were available in all controls and of the pulmonary valve were available in 34 (74%) controls. The hemodynamic changes of the women with AS, PAV and the controls are presented in Table 2 and of the women with PS, PPV and the controls in Table 3. The course of peak Doppler gradients of all groups are presented in Fig. 1. The peak and mean gradient increased by an average of 21 ± 3% and 24 ± 3% respectively in women with AS and increased by an average of 31 ± 3% and 31 ± 3% respectively in women with PAV during pregnancy compared to preconception values. No significant difference in increase of peak and mean gradient was found between women with AS and PAV

Table 1
Baseline characteristics (prior to pregnancy) of the study groups.

	AS (n = 22)	PAV (n = 10)	PS (n = 13)	PPV (n = 21)	Controls (n = 46)
Age at conception (*mean ± SD*)	27.9 ± 4.4	29.5 ± 5.0	27.4 ± 4.4	28.7 ± 42	29.8 ± 4.2
BMI (*mean ± SD*)	23.7 ± 2.8	23.0 ± 2.2	23.2 ± 4.5	25.0 ± 3.1	23.4 ± 3.8
Cardiac medication use prior to pregnancy[a] (N(%))					
Beta-blocker	4 (20)	2 (20)	1 (8)	3 (14)	0 (0)
Echocardiographic parameters (N(%))					
Pulmonary valve regurgitation[b]	0 (0)	0 (0)	7 (54)	6 (29)	
Aortic valve regurgitation[b]	4 (18)	0 (0)	0 (0)	3 (14)	
LV systolic dysfunction[c]	3 (14)	0 (0)	0 (0)	2 (10)	
RV systolic dysfunction[d]	2 (9)	2 (20)	4 (31)	11 (52)	

AS, aortic valve stenosis; LV, left ventricle; PAV, prosthetic aortic valve; PPV, prosthetic pulmonary valve; PS, pulmonary valve stenosis; RV, right ventricle.

[a] Available one year before pregnancy.
[b] Moderate or severe regurgitation [11].
[c] Ejection fraction < 45%.
[d] TAPSE < 17 mm.

(p = 0.366 and p = 0.599 respectively). In the pulmonary valve group, no increase in peak gradient or mean gradient during pregnancy compared to preconception occurred. In the control group, the peak gradient of the aortic valve and pulmonary valve increased by an average of 35 ± 4% and 27 ± 4% respectively during pregnancy compared to preconception and postpartum. Preconception values and postpartum values were comparable in all groups. AVA was measured at all times points in 50% of women with AS and EOA was measured in 70% of women with PAV. Except for one woman with a PAV (see Cardiovascular complications during pregnancy and neonatal outcome), no pathological valve obstruction was observed at preconception, during pregnancy or postpartum. When corrected for heart rate, peak and mean gradient showed no significant increases during pregnancy in women with VHD.

In Supplementary Table 1 we present the changes of cardiovascular parameters throughout pregnancy in women with aortic VHD, pulmonary VHD and controls. In all groups, heart rate increased significantly from preconception to second trimester and decreased again from third trimester to postpartum (p ≤ 0.001). In the control group, heart rate also increased significantly from the second to third trimester (p < 0.001). During pregnancy, the peak gradient/heart rate and mean gradient/heart rate did not differ between women who used β-blockers during pregnancy and those who did not. LVEF was normal in all groups at all moments (mean LVEF>50%) and did not change during pregnancy. Mean TAPSE increased from preconception to the second trimester in all groups (p ≤ 0.005). During pregnancy, only in women

with pulmonary VHD a decrease of TAPSE was observed (p = 0.005). Mean TAPSE was significantly lower at all moments in women with pulmonary VHD compared to women with aortic VHD and controls (<20 mm vs. ≥23 mm, p < 0.001).

3.3. Cardiovascular complications during pregnancy and neonatal outcome

Primary cardiovascular events were documented in 7.6% of the women with VHD and in none of the controls (p = 0.077). One woman with a PAV had valve thrombosis in the first trimester. She presented with progressive dyspnea and abnormal valve sounds on auscultation, no visible thrombus on echocardiography and a peak gradient of 52 mmHg (preconception 30 mmHg). Heparin therapy was required (peak gradient of 40 mmHg after treatment). One woman with a PAV developed a supraventricular tachycardia for which an increase of metoprolol dosage was needed. One woman with a PPV developed in both pregnancies symptomatic premature ventricular contractions for which an increase of metoprolol dosage was needed. Only in women with VHD NYHA class deterioration (≥2 classes) was observed (12.1% vs. 0%, p = 0.012). Beta-blocker use during pregnancy in women with VHD was reported in 16.7% at 20 weeks gestation and in 15.2% at 32 weeks gestation. Neonatal events were reported in 20.6% and 25.0% of the neonates of women with pulmonary and aortic VHD and in 8.7% of the neonates of controls. No neonatal deaths occurred. Birthweight was significantly lower in neonates of women with pulmonary and

Table 2
Hemodynamic changes of the aortic valve in pregnant women with aortic valve stenosis or valve replacement history versus pregnant controls.

	N	Pre-pregnancy	2nd trimester	3rd trimester	Postpartum
Aortic valve stenosis	Total n = 22				
Peak gradient (mmHg)	22	35.9 ± 20.4	41.9 ± 19.9*	40.6 ± 20.9	38.8 ± 22.8
Mean gradient (mmHg)	21	19.9 ± 10.4	23.3 ± 11.8*	23.5 ± 12.7	23.2 ± 15.8
Peak gradient/heart rate (mmHg)	20	0.47 ± 0.23	0.50 ± 0.22	0.46 ± 0.20	0.51 ± 0.23
Mean gradient/heart rate (mmHg)	20	0.26 ± 0.12	0.28 ± 0.12	0.27 ± 0.12	0.30 ± 0.14
Aortic valve area (cm²)	11	1.22 ± 0.50	1.14 ± 0.40	1.24 ± 0.49	1.20 ± 0.55
Aortic valve dimensionless velocity index	7	0.42 ± 0.11	0.49 ± 0.26	0.47 ± 0.20	0.45 ± 0.15
Prosthetic aortic valve	Total n = 10				
Peak gradient (mmHg)	10	34.9 ± 17.8	46.4 ± 26.9*	48.5 ± 22.9	35.9 ± 13.6
Mean gradient (mmHg)	10	20.1 ± 10.1	26.2 ± 13.4*	29.2 ± 14.3	21.6 ± 8.45
Peak gradient/heart rate (mmHg)	10	0.49 ± 0.32	0.59 ± 0.45	0.63 ± 0.42	0.52 ± 0.23
Mean gradient/heart rate (mmHg)	10	0.29 ± 0.18	0.33 ± 0.22	0.37 ± 0.24	0.31 ± 0.14
Effective orifice area (cm²)	7	1.10 ± 0.18	1.02 ± 0.16	0.96 ± 0.17	1.13 ± 0.12
Aortic valve dimensionless velocity index	7	0.36 ± 0.03	0.33 ± 0.05	0.32 ± 0.09	0.35 ± 0.03
Controls	Total n = 46				
AV peak gradient (mmHg)	46	6.48 ± 1.97	8.35 ± 2.34*	7.57 ± 2.32	6.48 ± 1.97#
AV peak gradient/heart rate (mmHg)	46	0.10 ± 0.03	0.12 ± 0.04*	0.10 ± 0.04^	0.10 ± 0.03

AV, aortic valve.

* Significant differences between pre-pregnancy and 2nd trimester (p < 0.0125).
^ Significant differences between 2nd trimester and 3rd trimester (p < 0.0125).
# Significant differences between 3rd trimester and postpartum

Table 3

Hemodynamic changes of the pulmonary valve in pregnant women with pulmonary valve stenosis or valve replacement history versus pregnant controls.

	N	Pre-pregnancy	2nd trimester	3rd trimester	Postpartum
Pulmonary valve stenosis	Total n = 13				
Peak gradient (mmHg)	13	28.1 ± 12.5	30.6 ± 13.4	29.9 ± 14.9	27.3 ± 13.7
Mean gradient (mmHg)	12	16.0 ± 7.89	17.3 ± 8.64	15.6 ± 8.75	14.5 ± 7.47
Peak gradient/heart rate (mmHg)	13	0.39 ± 0.18	0.39 ± 0.19	0.40 ± 0.24	0.40 ± 0.23
Mean gradient/heart rate (mmHg)	12	0.22 ± 0.11	0.22 ± 0.12	0.21 ± 0.14	0.21 ± 0.12
Prosthetic pulmonary valve	Total n = 21				
Peak gradient (mmHg)	21	22.4 ± 7.14	23.4 ± 7.82	23.0 ± 8.71	22.0 ± 8.22
Mean gradient (mmHg)	20	13.1 ± 4.82	13.4 ± 5.16	12.4 ± 4.51	13.0 ± 4.88
Peak gradient/heart rate (mmHg)	19	0.34 ± 0.13	0.32 ± 0.11	0.28 ± 0.11	0.32 ± 0.14
Mean gradient/heart rate (mmHg)	20	0.20 ± 0.08	0.18 ± 0.08	0.15 ± 0.06	0.19 ± 0.08[#]
Controls	Total n = 34				
PV peak gradient (mmHg)	34	4.15 ± 1.84	4.97 ± 1.64[*]	4.76 ± 2.20	4.15 ± 1.84
PV peak gradient/heart rate (mmHg)	34	0.06 ± 0.03	0.07 ± 0.02	0.06 ± 0.03	0.06 ± 0.03

PV, pulmonary valve.
[*] Significant differences between pre-pregnancy and 2nd trimester (p < 0.0125).
[#] Significant differences between 3rd trimester and postpartum (p < 0.0125).

aortic VHD compared to neonates of controls (3098 ± 500 g and 3102 ± 620 g versus 3622 ± 532 g, p < 0.001). Small for gestational age was documented in 14.7% of the neonates of women with pulmonary VHD, in 6.3% of the neonates of women with aortic VHD and in 2.2% of the neonates of controls. No significant differences were observed in neonatal events between women with pulmonary and aortic VHD and controls.

4. Discussion

This is the first study that evaluated serial changes in Doppler gradients and valve area in left- and right sided VHD during pregnancy, including pre-pregnancy and postpartum measurements. In women with aortic VHD, valve gradients increased during pregnancy and returned to baseline postpartum. Notable is that valve area remained

unchanged. Valvular gradients did not change significantly during pregnancy in women with pulmonary VHD.

Knowledge of the (normal) course of hemodynamic changes during pregnancy is required to correctly interpret the echocardiographic parameters used for the assessment of VHD. Previous studies evaluated hemodynamic changes in pregnant women with left sided VHD and reported an increase in valve gradients during pregnancy and a decrease after pregnancy. [6,14,15] However, echocardiographic assessment before pregnancy was lacking or the increase during pregnancy did not reach statistical significance. We found a significant increase in valve gradients in women with aortic VHD, however the decrease after pregnancy was not significant, probably due to the small study population. In women with aortic VHD and in the control group, aortic valve gradients increased from preconception to second trimester and remained stable in the third trimester. In addition, AVA and EOA remained
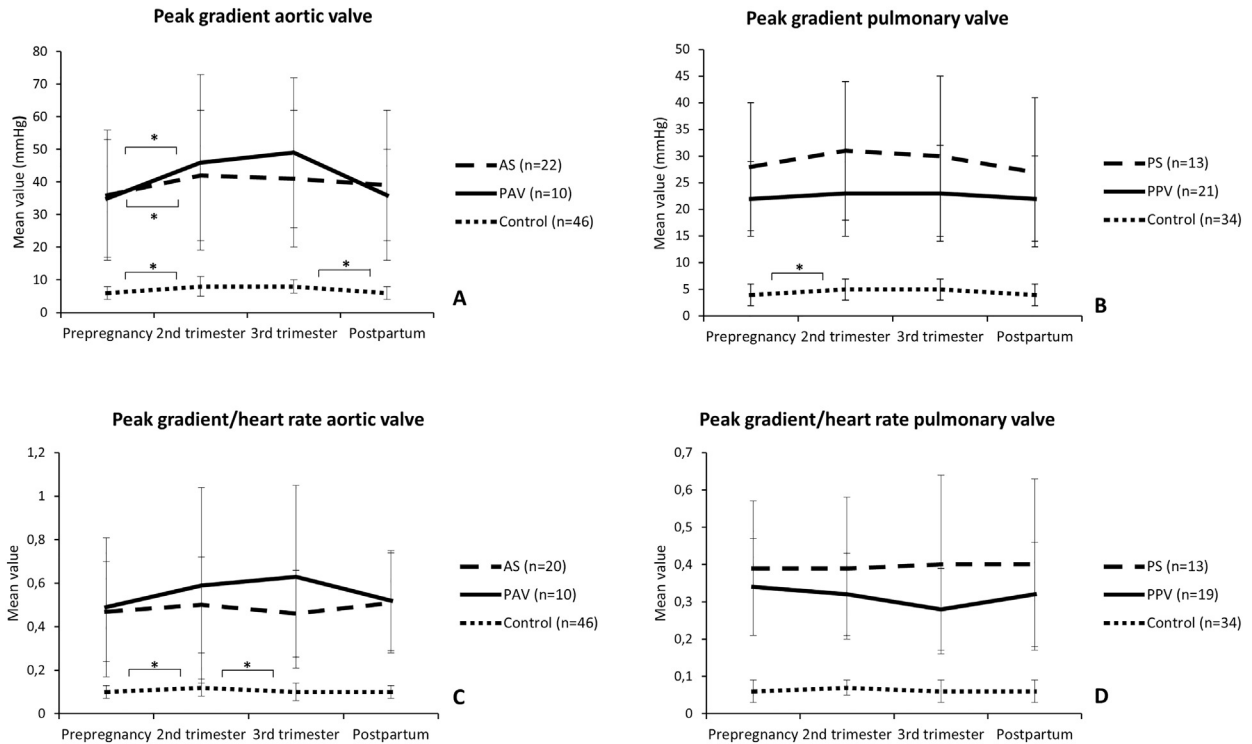

Fig. 1. The course of the peak Doppler gradients of women with aortic VHD (A), pulmonary VHD (B) and controls. The course of peak gradient/heart rate of women with aortic VHD (C), pulmonary VHD (D) and controls. AS, aortic valve stenosis; PAV, prosthetic aortic valve; PPV, prosthetic pulmonary valve; PS, pulmonary valve stenosis; VHD, valvular heart disease. *Significant difference between the specific time points (p < 0.0125).

unchanged in women with aortic VHD which is in line with the existing literature [6,14,15]. The findings of our study suggest that the physiological increase of cardiac output and intravascular volume (causing hemodilution) during pregnancy leads to a physiological increase of valve gradients. We suggest that the degree of valve stenosis must preferably be estimated by valve area measurements during pregnancy in women with VHD. Heart rate increases during pregnancy and tends to cause underestimation of the gradient of outflow heart valves due to shorter ventricular filling time. However, after correction for heart rate (increased significantly), the peak and mean gradient did not decrease significantly during pregnancy. Apparently, the increase in stroke volume and intravascular volume during pregnancy (causing increased valvular gradients) supersedes the effects of heart rate on valvular gradients.

Investigation of the course of the pulmonary valve gradient in pregnant women has never been performed. Interestingly, our study showed that in the control group the gradients of the pulmonary valve increased from preconception to second trimester, but the gradients in women with pulmonary VHD remained unchanged. Besides heart rate, also ventricular function can influence Doppler gradients. Impaired ventricular function tends to lead to underestimation of Doppler gradients and this might be the explanation for not finding an increase in valve gradients in women with pulmonary VHD. Women with pulmonary VHD had a lower mean TAPSE compared to the control group (mean TAPSE <20 mm vs. ≥23 mm, p < 0.001) before and during pregnancy, suggesting that RV function is not sufficient to meet the increased demands of pregnancy leading to unchanged pulmonary valve gradients. The observation that the evolution of TAPSE during pregnancy in women with pulmonary VHD is different from the pattern seen in the healthy and aortic VHD women may also point into that direction. Underpowering and merely mild pulmonary VHD as explanation for the unchanged gradients seems less likely as the groups are of the same size as the women with aortic VHD and there was a significant increase in the gradients of the pulmonary valve of the control group. Furthermore, evidence is increasing that RV function plays an important role during pregnancy. RV dysfunction before and during pregnancy is associated with impaired uteroplacental circulation in women with CHD, even in left sided lesions [8,16–18]. This is, in turn, associated with maternal, fetal and neonatal risks [19]. These data underscore the notion that in women with pulmonary VHD and an impaired RV function, evaluation of RV functional changes during pregnancy might be important for the assessment of VHD and for the identification of higher risk pregnancies.

The findings of our study are useful for the assessment of VHD in pregnant women in daily practice and confirm previous limited studies. We were not able to distinguish normal changes of the valve gradients from pathological ones due to the occurrence of only one valvular complication in our study population. In this particular case, the peak gradient increased by 73% compared to the pre-pregnancy gradient. Further larger-scale studies are needed for to investigate the predictive value of changes in valve gradients during pregnancy.

4.1. Strengths and limitations

To the best of our knowledge, this is the first study that evaluated the complete physiological changes during pregnancy in women with pulmonary or aortic VHD and compared this with changes in pregnant controls. Due to the study protocol, pre-pregnancy data collection was retrospective. For this reason, missing data were unavoidable. Valve area was not available in all women due to unreliable measurements of the left ventricular outflow tract velocity. The study population was relatively small (yet the largest reported thus far), hampering more complex longitudinal data analyses. Furthermore the relatively small study population may have been the reason why we did not find an association between pulmonary valve gradient and RV function. Moreover, we were only able to analyze TAPSE as RV function parameter.

5. Conclusion

Physiological changes during pregnancy lead to increased Doppler gradients during pregnancy in women with aortic VHD, without changes in valve area. The same expected changes were not found in women with pulmonary VHD, probably caused by impaired RV function. Therefore, evaluation of RV function during pregnancy might be important to prevent possible underestimation of the degree of stenosis in these women. When possible, the degree of valve stenosis must be estimated by valve area measurements during pregnancy in women with VHD.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2019.11.118.

Declaration of competing interest

The authors report no relationships that could be construed as a conflict of interest.

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