

Outcome of pregnancy in patients with bicuspid aortic valve – a study of 89 patients (RCD code: VII-IV-1D.2o)

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Abstract

The changes in hemodynamics, as well as changes in the aortic media during pregnancy, put the women with bicuspid aortic valve (BAV) and significant aortic stenosis (AS) and/or dilated aortic roots at risk for complications during this period. From 1988–2014, 89 pregnant patients with BAV, mean 26.8 ± 4.6 years, were observed. There were 52 patients with AS: 22 with mild AS, 30 with moderate to severe AS and 37 patients with aortic insufficiency (AI). Medical history, physical examination, NYHA class assessment, ECG and echocardiography were performed during each trimester (TR) of pregnancy and after delivery. During pregnancy all patients with mild AS remained in NYHA class I. All of them delivered vaginally healthy babies on term. Patients with moderate to severe AS in I TR remained in NYHA class I-II, in 6/30 patients clinical deterioration was observed within III TR. Seventeen women with severe AS delivered by cesarean section, the remaining vaginally. In the group of IA clinical deterioration was observed in III TR in 5/37 patients with severe AI, enlarged left ventricle (LV) and depressed systolic function. Six of them delivered by cesarean section, the remaining vaginally. Conclusions: Patients with mild AS tolerate well the increased cardiovascular demand of pregnancy. In patients with severe AS pregnancy intensifies the hemodynamic disorders. Volume overload of pregnancy is well tolerated in patients with mild and moderate IA. Cardiac complications can be expected in patients with severe IA, LV enlargement and impaired systolic function. In the observed group of BAV patients there was no pregnancy-associated dissection. JRC D 2014; 2 (1): 9–14

Key words: bicuspid aortic valve, aortic stenosis, aortic insufficiency, pregnancy, dissection

Background

Bicuspid aortic valve (BAV) is a congenital heart disease, occurring in 1–2% of the general population, with a male predominance of approximately 4:1 [1]. BAV may be functionally normal or it may be stenotic and/or regurgitant. BAV is the most common cause of isolated valvular aortic stenosis (AS) in adults and the most common cause of isolated aortic insufficiency (AI). Dilation of the ascending aorta is likely to coexist independently of valvular function [1–3]. Complications can include besides AS or AI, also endocarditis, aortic aneurysm formation, and aortic dissection. Despite the potential complications, 2 large contemporary series have demonstrated that life expectancy in adults with BAV disease is not shortened when compared with the general population [4]. The most common abnormality is dilation of the tho-

racic aorta. The thoracic aorta shows decreased fibrillin, elastin fragmentation, and apoptosis [1,2,4]. Deficient fibrillin-1 results in smooth muscle cell detachment, matrix disruption, and cell death [2]. BAV is also known to coexist with other congenital defects, such as coarctation of the aorta (the most common, at least 20% of cases and perhaps up to 85%) [5,6], Shone's syndrome with multiple left-sided lesions of inflow and outflow obstruction [7], Williams syndrome with supravalvular stenosis, Turner syndrome with coarctation of the aorta [8], ventricular septal defect, patent ductus arteriosus, atrial septal defect. There are also some reports suggesting the involvement of coronary arteries – single coronaries or reversal of coronary dominance [9]. Although more studies are required before genetic screening will have a role, clinical studies have reported a 9–10% prevalence of BAV in first-degree relatives of patients with BAV [10,11]. In the current era, trans-

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Table 1. Echocardiographic data of patients with BAV and aortic stenosis (AS) during pregnancy

	Mild SA		Moderate to severe SA	
	n = 22		n = 30	
	Range	Mean ±SD	Range	Mean±SD
AVA (cm ²)	1.6–2.0	1.8±0.20	0.5–1.5	1.1±0.45
Mean gradient (mm Hg)	13.0–31.0	20.5±7.2	33.4–91.0	55.1±11.2
Peak gradient (mmHg)	21.0–44.0	31.3±12.5	60.0–152.0	90.6±20.9
LVEDS (cm)	2.3–4.3	3.24±0.40	1.9–5.3	3.15±0.85
LVEDD (cm)	4.6–6.2	5.4±0.45	3.7–7.0	5.30±0.88
LAD (cm)	3.0–3.8	3.5±0.24	2.4–5.2	3.9±0.75
EF (%)	58.0–84.0	68±7.8	47.0–84.0	67.2±11.6
SV (ml)	57.0–98.0	78.2±10.2	41.0–102.3	76.1±21.6
CO (l/min)	4.2–9.1	7.5±1.4	3.6–9.2	6.3±1.6

AVA – aortic valve area; LVEDS – left ventricular end-systolic diameter; LVEDD – left ventricular end-diastolic diameter; LAD – left atrium diameter; EF – ejection fraction; SV – stroke volume; CO – cardiac output

thoracic echocardiography usually confirm the diagnosis. When adequate echocardiographic images are obtained, sensitivities and specificities of 92% and 96% are reported for detecting BAV anatomy. Echocardiographic diagnosis can be difficult in patients with heavily calcified valves [12]. In BAV disease, the aortic annulus, sinus, and proximal ascending aorta are larger than in adults with normal valves [13]. The prevalence of ascending aorta dilation (>40 mm) was reported as 15% (in the Olmsted County study) [14]. Dilation of the ascending aorta was an independent risk factor for ascending aorta surgery. The most dangerous complication is aortic dissection, primarily due to the high associated mortality rate. The presence of aortic dilation places affected patients at 6 to 10 times greater risk of aortic dissection compared to general population [15,16]. The reported rate of this complication varies from 4% [17] to even a lower risk – 0.1% per patient-year [18] or 0% [14]. Endocarditis is more common in BAV. The incidence of infective endocarditis in BAV patients was reported earlier from 10 to 30%. Currently, the estimated incidence is 0.16% per year in unoperated children and adolescents. In adults, the two large case series by Tzemos and Michelena give an incidence of 0.3% and 2% per year, respectively [4, 14,17,18]. The outcome in BAV patients with infective endocarditis tend to be worse than in those with normal valves.

The natural history of BAV has been evaluated several cohort studies. It is known to be variable and of course somewhat dependent on associated abnormalities. It can range from severe aortic stenosis in childhood to asymptomatic disease until old age [19].

Women with BAV should be counseled regarding potential risks and treatment prior to and during pregnancy. The changes in hemodynamics, as well as changes in the aortic media during pregnancy, put the women with BAV and significant aortic stenosis and/or dilated aortic roots at risk for complications during this period.

Material and Methods

During the period of 26 years (from 1988 to 2014) 89 pregnant patients with bicuspid aortic valve, aged 18–42, mean 26.8 ±4.6 years, were observed. There were 52 patients with aortic stenosis (AS): 22 with mild AS (AVA 1.6–2.0 cm²), 30 with moderate to severe AS (AVA 0.5–1.5 cm²) and 37 patients with aortic insufficiency (AI). Medical history and physical examination, NYHA class assessment, ECG and echocardiography were performed during each trimester (TR) of pregnancy and 6–12 weeks after delivery. Standard echocardiographic examination was performed using an electronic ultrasound beam with frequency of 2.5 or 3.5 MHz (Toshiba Power Vision 6000, Vivid GE 7).

Results

Aortic stenosis

During pregnancy all patients with BAV and mild AS remained in NYHA functional class I. Echocardiographic monitoring revealed good adaptation to the volume overload during pregnancy. Left ventricular end-systolic diameter (LVEDS), left ventricular end-diastolic diameter (LVEDD), stroke volume (SV), cardiac output (CO), left atrium diameter (LAD) peak and mean aortic gradients increased significantly between I and II trimester (TR), II and III TR, I and III TR (p<0.01), and decreased after delivery (p<0.05). There were no changes in ejection fraction (EF) during pregnancy and after delivery (Table 1). All these patients were in sinus rhythm, and no medical treatment was required. All of them delivered on term (37–40 weeks) vaginally healthy babies, with mean birth weight 3.700 ±480 g.

Table 2. Echocardiographic data of patients with BAV and aortic insufficiency (IA) during pregnancy

	n = 37	
	Range	Mean±SD
Mean gradient (mmHg)	3.0–24.8	11.2±5.8
Peak gradient (mmHg)	5.9–48.0	23.6±10.8
LVESD (cm)	2.5–4.8	3.65±0.60
LVEDD (cm)	4.2–6.6	5.5±0.82
LAD (cm)	2.4–4.1	3.4±0.35
EF (%)	47–76	61.5±6.5
SV (ml)	5.00–138.0	97.8±30.3
CO (l/min)	4.39–11.8	8.1±2.6

LVESD – left ventricular end-systolic diameter; LVEDD – left ventricular end-diastolic diameter; LAD – left atrium diameter; EF – ejection fraction; SV – stroke volume; CO – cardiac output

Patients with **BAV and moderate to severe AS** in the I TR remained in NYHA class I-II, in 6/30 (20%) patients a clinical deterioration with a decline in ≥ 2 NYHA functional classes within III TR was observed. These 6 patients presented with dyspnea, decreased exercise tolerance and ventricular arrhythmia (exacerbation of ventricular extrasystolia). They were treated medically with betablockers (5 patients) and mexiletine (1 patient). Echocardiography pointed out abnormal adaptation to volume overload during pregnancy. In this group of patients, there was no significant increase of LVEDD, LVESD, CO, SV between II and III TR. The maximum pressure gradient across the aortic valve ranged from 60 to 152 mm Hg, and was greater by 20 to 42 mm Hg comparing to the post-delivery values ($p < 0.001$) (Figure 1). EF didn't change significantly during pregnancy nor after delivery (Table 1). Seventeen women with BAV and severe SA delivered by cesarean section (17/30, 56.7%), the remaining vaginally. All patients delivered healthy babies with normal birth-weight 3.560 ± 380 g. There were 2 preterm deliveries, in 35 and 36 week respectively.

Aortic insufficiency

In the group of **BAV and IA** patients, clinical deterioration was observed in III TR of pregnancy in 5/37 (13.5%) with severe IA, enlarged left ventricle (LV) and decreased left ventricular systolic function ($EF \leq 50\%$). These 5 pregnant presented with exertional dyspnea (NYHA III) and required diuretic therapy.

The significant increase of LVEDD, LVESD, CO, LAD was noticed during pregnancy. There were no statistical differences of SV values between II and III TR. Additionally, we noted a significant increase of EF and fractional shortening (FS) postpartum comparing to pregnancy period ($p < 0.05$). Selected echocardiographic data during pregnancy are presented in table 2.

Six of them (6/37, 16.2%) delivered by cesarean section due to obstetric indications, the remaining 31 vaginally. There were 2 pre-

term deliveries in this group of patients, all in 36 week. The mean birth-weight was 3.860 ± 340 g.

The aortic diameter measured in the total BAV group (ranging from 28 to 44 mm) didn't change during pregnancy. In two patients with BAV and severe IA, this diameter was greater than 40 mm, 42 and 44 mm, respectively. Three patients (3/89; 3.37%) had hypertension, treated successfully with beta blocker. There was no aortic dissection, nor endocarditis. There were no congenital heart diseases in the offspring.

Discussion

Progress in medical and surgical treatment has resulted in larger numbers of women with congenital heart disease surviving to child-bearing years and proceeding with pregnancy [20]. An isolated, functionally normal BAV is likely to be unrecognized in women of child-bearing age, because auscultatory signs are inconspicuous. BAV in parturients may carry a significant risk for cardiac complications and may even lead to maternal and fetal death [2]. Pre-pregnancy counseling and evaluation of cardiac function and aortic root are necessary. Transthoracic echocardiography usually confirm the diagnosis. Due to the natural history of BAV to lead to heavily calcified stenotic valves, the utility of echocardiography can be limited [21]. In BAV disease, the aortic annulus, sinus, and proximal ascending aorta are larger than in patients with trileaflet valves [13, 22]. Aortic dilatation has been documented in childhood, which suggests that this process begins early in life. Information on the rate of progression of aortic disease associated with BAV varies widely, with studies reporting ≈ 0.3 – 1.1 mm per year [23]. The prevalence of ascending aorta dilation (>40 mm) was reported as 15% (in the Olmsted County study) [15]. Dilatation of the ascending aorta was an independent risk factor for ascending aorta surgery. A great majority of patients with BAV are asymptomatic.

Women with BAV should be counseled regarding potential risks and therapeutic options prior to and during pregnancy. Potential risks that should be discussed include heritable congenital heart disease, aortic enlargement or dissection, and complications of aortic stenosis and/or aortic regurgitation. The symptoms of the BAV tend to worsen with increasing stenosis severity. The increased cardiac output of pregnancy adds volume overload to an already pressure-loaded left ventricle. The main symptoms are exertional dyspnea, syncope, arrhythmia, and chest pain. Maternal arrhythmias were reported in 2.4%, heart failure in 7%, myocardial infarction, stroke or cardiovascular mortality in 2.5%, premature delivery in 8.3%, fetal mortality in 0%, perinatal mortality in 0.6% and fetal congenital heart disease in 4.1% [24]. In the group of patients with mild AS volume overload of pregnancy is tolerated well. Contrary, about 10–30% of pregnant women with BAV and severe AS may experience cardiovascular deterioration [2, 25–27]. In rare instances, women will develop progressive symptoms during pregnancy and require either balloon valvuloplasty or valve surgery. Cardiac surgery should be avoided, if possible, during pregnancy. The maternal risk is about the same as in non-pregnant women, but cardiopulmonary by-pass during pregnancy poses problems for the fetus. Both interventions should be performed only when necessary –

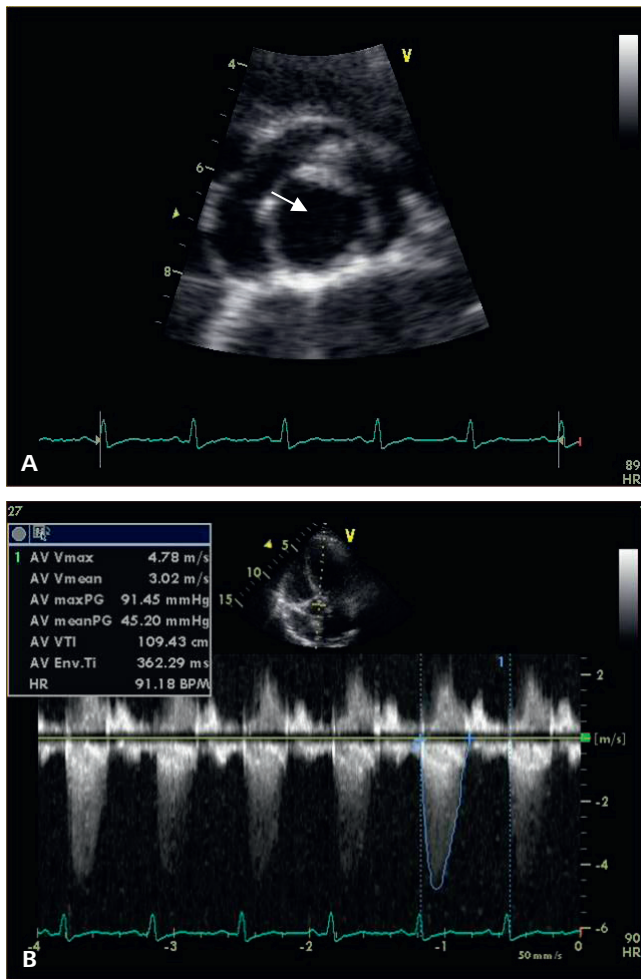


Figure 1. Transthoracic echocardiogram of a pregnant patient (22 week of gestation) with bicuspid aortic valve and severe aortic stenosis. **A.** Parasternal short axis view of aortic valve (arrow). **B.** Continuous wave Doppler calculations: max. gradient – 91.5 mm Hg, mean – 45.2 mm Hg, aortic valve area – 0.7 cm²

refractory NYHA III or IV class symptoms [4, 28, 29]. In spite of severe AS, the majority of pregnant patients did not present any significant symptoms. As already referred to in our previous study, an unfavorable prognostic factor was identified as a lack of increase of stroke volume and cardiac output [27]. It is documented by Tzemos et al., that women with congenital AS have a higher frequency of late cardiac events in the follow-up after pregnancy compared to those who have never been pregnant [30].

Aortic incompetence (AI) is relatively common in BAV and is often independent of aortic stenosis [19]. Approximately 15–20% of BAV have incomplete valve closure and present at age 20–40 with asymptomatic diastolic murmur, cardiomegaly or symptoms due to AI. One cohort of 118 BAV patients found that of 70 patients without aortic stenosis, 40% had moderate to severe aortic regurgitation [19,31,32]. The mechanisms of AI in children are usually due to prolapsing cusps, postvalve surgery or endocarditis, myxoid degeneration of the valve, while as the patients age dilatation of the ascending aorta can lead to a functionally regurgitant valve [32]. Pregnancy in AI patients with normal LV systolic function

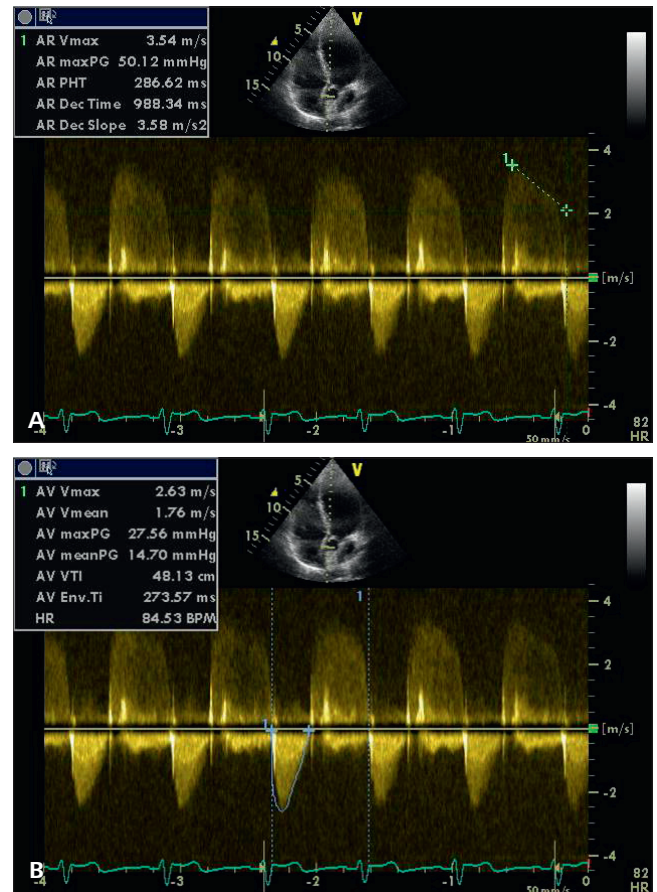


Figure 2. Transthoracic echocardiogram of a pregnant patient (28 week of gestation) with moderate aortic insufficiency (AI) and mild aortic stenosis. **A.** Continuous wave Doppler calculations: AI pressure half time (PHT) – 286 ms. **B.** Continuous wave Doppler calculations: peak gradient – 27.6 mm Hg, mean – 14.7 mm Hg

and NYHA I-II class is usually well tolerated. The fall in systemic vascular resistance during pregnancy and tachycardia which shortens diastole decrease the degree of regurgitation. Contrarily, symptomatic patients (NYHA III-IV class) with severe AI and EF < 40% are at high risk for developing cardiac complications during pregnancy [33]. In our group, in 5/37 (13.5%) patients with severe IA, enlarged LV and EF ≤ 50% clinical deterioration was observed in III TR, those patients required diuretic therapy. Fetal ultrasound is recommended when the mother has bicuspid aortic valve, because the risk of congenital heart defect in the offspring is estimated about 6–7%.

Heightened awareness of the association between BAV and ascending aortopathy and dissection has led to increasing concern regarding the safety of pregnancy in this population [15]. Pregnancy-related increase in heart rate, blood pressure and stroke volume result in increased aortic stress, which may promote aortic dilation or dissection. In pregnant patients proximal aortic dilation can progress to ectasia or aneurysm, the risk of aortic dissection may be increased. Aortic root enlargement > 40 mm or an increase of aortic root size during pregnancy in patients with BAV and Marfan syndrome is associated with a considerable risk for the occurrence of type A dissection [34]. The presence of aortic root dilation can

indicate risk, but dissection can occur even in the absence of the dilation [35]. A comparison between BAV and normal aortic valve patients showed that, although BAV patients had a higher rate of aortic growth (1.9 vs 1.3mm/year), the incidence of rupture and dissection was similar [23]. Type A dissection carries the highest risk of life threatening event and require early surgical intervention. The mortality rate for unrepaired Type A dissection is 1% per hour during the first 24 hours after the onset of symptoms and 75% at second week if left untreated [36].

All pregnant women with thoracic aortic dilatation should maintain strict blood pressure control to prevent stage 2 hypertension (blood pressure systolic ≥ 160 or diastolic ≥ 100 mm Hg) and slow the progression of aortopathy. Angiotensin converting enzyme inhibitors and angiotensin receptor blockers are contraindicated during pregnancy. The guidelines did not address the issue of beta blockers in pregnancy in patients with BAV, only to those with Marfan syndrome. But it seems reasonable to treat with beta blockers pregnant patients with BAV and dilation of aorta. In the observed group of BAV patients the maximum aortic root diameter was 44 mm. There were only two patients (2.25%) with aortic root diameter >40 mm. The outcome of the majority of our patients with BAV was good, there were no dissections, no maternal or fetal/neonatal deaths. Pregnancy in our group of patients was not associated with progressive dilatation of the aortic root, aorta surgery or aortic valve replacement. This was consistent with the report of Mc Kellar and al. concerning the Olmsted County Study [15]. The findings of their study suggest that the risk of pregnancy-associated dissection in the BAV patients is low [15]. In pregnant patients with aortic dilatation, echocardiography should be done at 4–8 weeks intervals throughout the pregnancy until 6 months postpartum [28,29]. Magnetic resonance is recommended for imaging the aortic arch, descending and abdominal aorta. It is considered to be safe (without gadolinium) from 12 weeks of gestation [29,37]. Transesophageal echocardiography is also an alternative method for thoracic aorta assessment. Later after delivery, annual (at a minimum) cardiac imaging is recommended for patients with significant valve lesions or those with aortic root diameters ≥ 40 mm. In patients without significant valve lesions and aortic roots diameters <40 mm, cardiac imaging every 2 years may be adequate [28]. Aortic root size should be referenced to body surface area, especially in those patients where body size is important, such as women and patients with Turner syndrome – the value of $2.1 \text{ cm}^2/\text{m}^2$ is considered the upper limit of normal [38]. The European Society of Cardiology guidelines recommend pre-pregnancy surgery for an aortic size >50 mm in patients with BAV [29]. Delivery at a center experienced with high-risk heart diseases is recommended for patients with more than mild AS or dilated aortic diameter (>40 mm) [28]. Controlled vaginal delivery is preferable in the majority of patients. Cesarean section is recommended only for obstetric reasons or in the presence of severe cardiovascular disease (aortic dissection, severe AI, critical AS, or in the presence of oral anticoagulation). According to recent guidelines, endocarditis prophylaxis is not indicated during uncomplicated vaginal or cesarean delivery [29].

Conclusions

Patients with BAV and mild SA tolerate well the increased cardiovascular demand of pregnancy. In BAV patients with severe SA, pregnancy intensifies the hemodynamic disorders. Volume overload of pregnancy is well tolerated in BAV patients with mild and moderate IA. Cardiac complications can be expected in BAV patients with severe IA, with LV enlargement and impaired systolic function. In the observed group of BAV patients there was no pregnancy-associated dissection.

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