



Risk of Complications During Pregnancy in Women with Congenital Aortic Valve Stenosis

a report by

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The prevalence of heart disease in pregnant women is estimated to be between 0.1 and 4%; although the prevalence has not changed for decades, the relative contribution of different types of heart disease varies according to the study population and the study period. Nowadays, in developed countries the largest group of females with an underlying heart disease consists of women with congenital heart defects (70–80%), followed by patients suffering from valvular sequelae of rheumatic fever.¹ Congenital heart defects occur in approximately 0.8% of newborns. Progress in medical, interventional, and surgical treatment has largely improved the outcome for these children, leading to an excellent survival into adult life.^{2–4} In particular, congenital aortic valve stenosis (AS) accounts for about 5% of all congenital heart defects. Despite a male predominance (the male–female ratio is between 3:1 and 5:1), AS is considered to be the most common cause of left ventricular outflow tract (LVOT) obstruction in young women. These women reach reproductive age and want to become pregnant. Unfortunately, underlying heart disease has become the major cause of non-obstetrical maternal death and accounts for 15% of all pregnancy-related mortality in Western countries.^{5,6} The level of risk incurred by pregnancy depends on functional status and the specific cardiac condition, both of which determine the ability of the cardiovascular system to adapt to the physiological changes of pregnancy.

Morphological, Epidemiological, and Hereditary Aspects of Congenital Aortic Stenosis

Congenital obstruction of the LVOT may involve the subvalvular, valvular, or supra-ventricular part of the outflow tract complex. Stenosis due to a congenital malformation of the aortic valve is the most common form of LVOT obstruction, found in more than 50% of cases. Abnormal

development of the valve commissures results in unicuspid, bicuspid, tricuspid, or even quadricuspid valves. The most common abnormality is the bicuspid valve, which accounts for more than 95% of congenital AS. A bicuspid valve seems to be an isolated defect, but in 20% of patients associated defects can be found, including coarctation of the aorta (most common), patent ductus arteriosus, and ventricular septal defect (VSD). Moreover, a bicuspid valve is found in approximately 50% of patients with coarctation of the aorta. These two lesions are the most common cardiac anomalies found in patients with Turner syndrome. In about one-third of patients, the level of the obstruction is subvalvular. Subvalvular stenosis represents a spectrum of anomalies ranging from a simple fibrous membranous to a tunnel-like fibromuscular band. It can be found as an isolated lesion, but in 60% of cases it is related to other heart defects, particularly to multilevel LVOT obstruction. Other associated lesions include VSD, coarctation of the aorta, and the Shone complex (coarctation of the aorta, parachute mitral valve, supra-ventricular mitral ring, sub-AS).

Finally, supra-ventricular AS is found to be the rarest obstructive lesion of the LVOT (less than 10%). The defining feature of this condition is aortic narrowing above the level of the aortic valve. In more than one-third of cases, the aortic valve is also abnormal; association with a subvalvular obstruction (20% of cases), coarctation of the aorta, and mitral valve stenosis. It appears uncommon as an isolated defect and is mostly found as a mild form when detected during adulthood. More often, a supra-ventricular stenosis in adults is encountered as a residual lesion following surgical repair in childhood, or as one of the characteristics of Williams syndrome (60% of cases). Supra-ventricular stenosis might also occur in familial form (7%) and even sporadically (30%).

Mothers with congenital heart defects have an approximately 6–8% risk of passing them on to their children—a 10-fold increase in comparison with the general population, which is probably due to multifactorial inheritance.⁷ However, in the case of a monogenetic anomaly such as Williams syndrome and some familial forms of supra-aortic stenosis, an autosomal dominant pattern is present, affecting 50% of the offspring. Therefore, genetic counseling should be incorporated when discussing child wish.

Pathophysiological Changes During Pregnancy and Labor

In normal pregnancy, both plasma volume and cardiac output increase steadily until the end of the second trimester, when cardiac output reaches its plateau at 30–50% above pre-pregnancy levels.^{8,9} A higher stroke volume and, to a lesser extent, an increase in heart rate (up to 10–15 beats per minute) are responsible for the increase in cardiac output. Simultaneously, systemic vascular resistance and blood pressure decrease. The latter usually lowers to its nadir at about 20 weeks' gestation, and returns to pre-pregnancy levels at term. In



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severe AS, stroke volume remains fixed and the increase in cardiac output is strongly limited, which leads to an elevation of ventricular systolic and diastolic filling pressures. These patients become very sensitive to acute changes in preload and afterload, so that myocardial ischemia and heart failure can occur.

Labor, particularly at the second stage, is characterized by a further increase in cardiac output by 40–50% through a pain-induced sympathetic response and through auto-transfusion by uterine contractions. Moreover, soon after delivery, decompression of the inferior vena cava increases the preload. Again, these changes put women with LVOT obstruction at a higher risk of pulmonary edema during the later stages of labor and shortly after delivery. Finally, changes in the extracellular matrix of the tunica media of the aorta can occur, leading to increased vascular compliance. The latter, in combination with cystic media necrosis (as seen in patients with a bicuspid aortic valve or in Marfan's syndrome), clearly increases the risk of aortic dissection, even several months after delivery.

Risk of Pregnancy in Congenital Aortic Stenosis

In earlier observations, mortality among pregnant women with severe AS was estimated to be 17%, whereas fetal mortality occurred in up to 30%.^{10,11} Two small cohorts confirmed this burden of maternal and fetal adverse events, especially in cases of moderate to severe stenosis, with an emphasis on the functional decline of the mother and a greater incidence of intra-uterine growth retardation and prematurity versus matched controls.^{12,13} As a consequence of these high mortality rates and the potential risk of chest pain, heart failure, and collapse, as well as sudden death during pregnancy and delivery and shortly after delivery, most physicians discouraged patients with significant AS from becoming pregnant or proceeding with existing pregnancies.

In the past few decades, there has been increasing interest in pregnancy in women with underlying heart disease, and researchers have sought to calculate a risk score that could guide physicians regarding appropriate counseling tailored to the individual patient. Clark et al. developed a mortality risk prediction based on the underlying condition (see *Table 1*).^{8,14} This table represents a synthesis of maternal mortality estimates for various types of heart diseases, divided into low-, intermediate-, and high-risk groups. Group 1 includes conditions that should have negligible maternal mortality (less than 1%) if proper care is provided. Group 2 contains a spectrum of diseases with an estimated risk of maternal mortality of 5–15%. Mild to moderate AS, regardless of either functional class or symptoms, is situated in this category. The authors consider the risk acceptable in individual cases with appropriate counseling and care and a tight follow-up regimen. Patients in group 3 have a mortality risk of more than 25% and should be advised to avoid or to terminate pregnancy. Severe AS and poor functional class (New York Heart Association (NYHA) classes III or IV) are in this group. In contrast, in a large prospective trial of 599 pregnancies in Canadian women with varying underlying heart disease (74% congenital, 22% acquired, and 4% arrhythmic), a scoring system has been developed and validated, irrespective of the underlying heart disease.^{15,16} The risk factors that predict independently adverse maternal events (pulmonary edema, sustained arrhythmia, stroke, cardiac arrest, or cardiac death) are summarized in *Table 2*. The most significant predictor was left ventricular dysfunction (defined as an ejection fraction below 40%). The other risk factors were: poor functional class (NYHA classification more than II); cyanosis before pregnancy (oxygen saturation less than 90%); pre-conception cardiac events such as stroke, transient ischemic attack,

Table 1: Mortality Risk Associated with Pregnancy

Groups	Underlying Cardiac Disease	Mortality Risk
Group 1	Atrial septal defect, uncomplicated	<1%
	Ventricular septal defect, uncomplicated	
	Patent ductus arteriosus, uncomplicated	
	Pulmonary/tricuspid valve disease	
	Repaired tetralogy of Fallot	
	Bioprosthetic valve (porcine/human)	
	Mitral stenosis, NYHA class I and II*	
Group 2	Mitral valve stenosis with atrial fibrillation	5–15%
	Mechanical valve prosthesis	
	Mitral valve stenosis, NYHA class III and IV*	
	Aortic valve stenosis	
	Coarctation of the aorta, uncomplicated	
	Unrepaired tetralogy of Fallot	
	Previous myocardial infarction	
Group 3	Pulmonary arterial hypertension	25–50%
	Coarctation of the aorta, complicated	
	Marfan syndrome with aortic dimension >40mm	

* New York Heart Association classification of cardiac disease.

Table 2: Risk Factors for Cardiac Events for Women with Heart Disease During Pregnancy

Risk factors	Prior cardiac event	Symptomatic arrhythmia Stroke or transient ischemic attack Pulmonary edema/heart failure
	Poor functional class pre-pregnancy or cyanosis	NYHA class III/IV* Oxygen saturation <90%
	Left heart obstruction	Mitral valve area <2cm ² Aortic valve area <1.5cm ² and/or LVOT** peak Doppler gradient >30mmHg
	Left ventricular dysfunction	Ejection fraction <40%
Risk index	0 risk factors	5%
	1 risk factor	27%
	2 risk factors	75%

* New York Heart Association classification of cardiac disease.

** Left ventricular outflow tract.

pulmonary edema, and symptomatic arrhythmia; and, finally, left heart obstruction at the level of the mitral valve or the LVOT. The risk for cardiac complications in pregnancies with no risk factors, one risk factor, and more than one risk factor was 5%, 27%, and 75%, respectively.¹⁵

According to Siu et al., a moderate aortic valve stenosis (valve area <1.5cm) is already a predictor for a higher incidence of both maternal and fetal adverse events. However, a more recent observational study of the same group found substantial problems only when the aortic valve stenosis was defined as a valve area <1cm; they reported 6% maternal events and 12% fetal events, as defined previously.¹⁷ No deaths were found among their series. The problems related to AS seem to occur not only during pregnancy, during labor, and after delivery, but also in the postpartum period. In a series described by Silversides et al., a high incidence (31%) of valve surgery during a follow-up period of nearly three years after the pregnancy was reported.¹⁷ This should be taken into account at the time of pre-pregnancy counseling.

Management Guidelines

Pre-pregnancy Counseling

Asymptomatic women with only a mild stenosis *in casu* aortic valve area >1.5cm and/or a mean Doppler gradient in the LVOT of less than 30mmHg can be considered low-risk and should have appropriate pre-pregnancy counseling in a specialized environment. However, they can generally be managed in a conservative way at their local hospital. AS patients with a valve area >1cm and/or a mean Doppler gradient in the LVOT of less than 50mmHg and preserved systolic left ventricular function will tolerate pregnancy well. In the absence of complications, the pregnancy can be followed in the local hospital, but a more specialized center is preferred for delivery.^{18,19} In all other cases (valve area <1cm), antenatal care and care during pregnancy should take place in a tertiary care clinic with a multidisciplinary approach involving geneticists, cardiologists, obstetricians, and anesthesiologists. In pre-pregnancy counseling, an exercise test is advised to rule out ST-T changes and arrhythmia. Patients with valve-related symptoms or extremely severe AS should be advised to delay conception until relief of the obstruction. Nevertheless, selection of valve prostheses for women of childbearing age is still a major issue. Bioprostheses are not as durable as mechanical prostheses, but eliminate the risks associated with anticoagulation for mechanical valves. Bioprosthetic valves do not seem to degenerate more rapidly during pregnancy, as was previously feared.²⁰ The Ross procedure, which has a better long-term outcome, is an attractive option for women of childbearing age.

Pregnancy

Asymptomatic pregnant women with severe AS have to be managed in a conservative way with bed rest, beta-blockers, and diuretics. However, in patients who develop alarming symptoms and who are resistant to medical treatment and reluctant to terminate their pregnancy, percutaneous balloon valvuloplasty or surgery before labor and delivery might be an option. However, aortic valve surgery is associated with a high risk of fetal loss (up to 30%), and, therefore, percutaneous valvuloplasty is mostly preferred.^{21,22} If the fetus is viable, a Cesarean section can be performed immediately before surgical valve repair or replacement.

Delivery

In most cases, vaginal delivery with assisted second stage of labor is recommended; this comprises low-dose epidural analgesia with a cardiostable drug, labor in left lateral decubitus to avoid aortocaval compression, and obstetric procedures such as vacuum extraction or forceps to shorten the second stage and to avoid repetitive Valsalva maneuvers. A Cesarean section is mainly preserved for obstetric indications; cardiac reasons for a Cesarean section include an aortic root dilatation of more than 4cm, aortic aneurysm,

or high risk of aortic dissection or rupture. Hemodynamic monitoring during labor and delivery is strongly recommended in women with moderate to severe aortic valve stenosis. Low-dose epidural anesthesia with adequate volume expansion to avoid a sudden decrease in systemic vascular resistance is allowed in these patients.²³ Although the American Heart Association (AHA)/American College of Cardiology (ACC) and European guidelines do not advise antibiotic prophylaxis in non-instrumented vaginal delivery or Cesarean section, most practitioners routinely provide antibiotics at the onset of labor. Indeed, bacteremia is reported in 2% of the patients, even after an uncomplicated vaginal delivery.²⁴

Anticoagulation During Pregnancy

In the absence of residual hemodynamic lesions, pregnancy and delivery are generally well tolerated after valve replacement. However, the need for anticoagulation therapy for mechanical valve prostheses represents a major problem. There are no randomized trials available to compare different anticoagulation regimens during pregnancy. Recommendations are largely based on extrapolations from data derived from series of non-pregnant patients and from small case series of pregnant patients. Substantial concern remains about the fetal safety of warfarin, since it crosses the placenta and might cause the typical warfarin embryopathy. However, the incidence of this embryopathy is still an issue for debate. The overall risk seems to be around 5% in patients who receive vitamin K antagonists between the sixth and 12th week, but seems to be significantly lower if the dose of warfarin is less than or equal to 5mg/day. On the other hand, a recent overview of the literature reported an increased risk of maternal thromboembolism when using heparin, even in anti-Xa adjusted doses.²⁵ Warfarin therapy is still the safest option for the mother and is associated with a 4% rate of maternal thromboembolism and a 30% rate of fetal loss. The strategy of substituting heparin for warfarin during the first trimester eliminates the risk of warfarin embryopathy, but doubles the risk of thromboembolism for the mother up to 9%. However, fetal loss rates are similar for any method of effective anticoagulation. Whatever the regimen of anticoagulation chosen during pregnancy, strict follow-up and frequent monitoring for appropriate dose adjustment are mandatory.¹⁹

In summary, most women with mild to moderate aortic valve stenosis may have a relatively low-risk pregnancy. Therefore, to identify these patients, pre-pregnancy counseling should be optimized, starting from adolescence. The latter gives the opportunity to tailor advice to the individual patient in order to prevent avoidable pregnancy-related risks. Related to the problems of pregnancy, women of reproductive age should also be informed about contraception. Finally, adequate care during pregnancy and delivery and in the postpartum period requires a multidisciplinary approach by cardiologists, obstetricians, geneticists, and anesthesiologists. ■

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