

# Outcome of Pregnancy in Women after Pulmonary Autograft Valve Replacement for Congenital Aortic Valve Disease

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**Background and aim of the study:** The pulmonary autograft has been recommended as the valve of choice for aortic valve replacement (AVR) in young women contemplating pregnancy. However, current information on maternal and perinatal outcome of pregnancy in women with pulmonary autograft valve replacement is limited.

**Methods:** Using a nationwide Dutch registry (CONCOR) and a local Belgian tertiary care center database, 17 women (age range: 18 to 45 years) with pulmonary autograft valve replacement were enrolled into the study. Twelve pregnancies were observed among five different women, including one miscarriage and one elective abortion.

**Results:** Clinically significant (non-)cardiac complications were documented in two of 10 completed pregnancies. Complications included: (i) placental abruption necessitating Cesarean delivery at 29

weeks' gestation, further complicated by postpartum hemorrhage; and (ii) preterm premature rupture of the membranes resulting in premature delivery at 29 weeks' gestation with postpartum demise of the immature born child. Two women reported primary female infertility, but both became pregnant after hormonal substitution therapy. Four women reported irregularities of their natural menstrual cycle (menorrhagia, dysmenorrhea, polymenorrhea, oligomenorrhea, or amenorrhea).

**Conclusion:** Successful pregnancy in women with pulmonary autograft valve replacement is possible, although serious and clinically significant events occurred during gestation. Infertility and menstrual cycle disorders appear to be more prevalent.

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The decision to perform aortic valve replacement (AVR) in women of childbearing age is difficult because no ideal valve is available. Mechanical valves are associated not only with the disadvantage of increased thrombogenicity but also with the requisite anticoagulation that promotes the risks associated with pregnancy for both mother and child, namely prematurity, birth defects, and neonatal mortality (1,2). On the other hand, bioprostheses have a high rate of early structural valve deterioration in young adults; indeed, earlier studies have suggested an acceleration

of valve deterioration during pregnancy (3,4), although is not reflected by current opinion (5-7).

A pulmonary autograft (Ross) procedure consists of autotransplantation of the pulmonary valve to the aortic position. Subsequently, an aortic or pulmonary homograft or a heterograft is placed in the pulmonary position (8). The pulmonary autograft is not thrombogenic and provides excellent valve hemodynamics (9); hence, several groups have suggested the pulmonary autograft procedure as the preferred method for AVR in young women contemplating pregnancy (10,11). However, information on pregnancy in women after the pulmonary autograft procedure is limited (11,12).

The primary objective of the study was to identify the magnitude of (non-)cardiac pregnancy risks in a contemporary cohort of women who had undergone pulmonary autograft valve replacement for congenital aortic valve disease. The secondary objectives were to assess the occurrence of infertility and menstrual cycle disorders in these patients.

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## Clinical material and methods

### Patients

In 2005, the Dutch CONCOR registry (CONgenital CORvitia; www.concor.net) and a local Belgian tertiary center database were reviewed for all women (age range: 18 to 45 years) who had received a pulmonary autograft valve replacement for congenital aortic valve disease. All women were regular visitors to the outpatient clinic of one of the six participating tertiary academic centers. The study protocol was approved by the institutional review board or ethics committee at each of the participating centers. Overall, 17 of the 20 identified women (85%) provided their written informed consent to participate in the study. The final study population included five women with one or more completed pregnancy (>20 weeks' gestation) after the pulmonary autograft procedure.

### Data acquisition

A detailed structured questionnaire was obtained from each patient by telephone. The results of the questionnaire were compared with obstetric data from medical records, when available. Data were collected on associated congenital cardiovascular anomalies, previous surgical/interventional procedures, medical history (as recorded by European Pediatric Cardiac Coding), age at inclusion, age at menarche, menstruation cycle (duration, regularity without hormonal substitution); primary amenorrhea (menarche not established at 16th birthday, in the presence of normal growth and secondary sexual development); secondary amenorrhea (absence of menstruation for >180 days after menarche in the absence of pregnancy, lactation or menopause); oligomenorrhea (menstrual bleeding at intervals >35 days), polymenorrhea (menstrual bleeding at intervals <24 days); menorrhagia (excessive or prolonged (>7 days) menstrual bleeding occurring at regular intervals characterized by loss of blood clots or development of anemia); infertility (>2 years of pregnancy attempts, investigated and documented by a gynecologist), miscarriages (spontaneous fetal loss before 20 weeks' gestation), and elective abortions. Detailed information regarding each completed pregnancy was also recorded according to the protocol, as described previously (13,14).

### Data analysis

A Clintrial data-entry program (Phase Forward, Waltham, Massachusetts, USA) was used to record data, which were then converted to SPSS (version 13.0; SPSS, Inc., Chicago, Illinois, USA). Descriptive statistics for nominal data were expressed in absolute numbers and percentages. After checking for normality, mean values and standard deviations were calculated

Table I: Characteristics at inclusion of women with pulmonary autograft valve replacement (n = 17).

Characteristic	No. of patients
Age at menarche (years)*	13 (10-17)
Cardiovascular interventions before	
Ross procedure <sup>+</sup>	15 (88)
Open aortic valvotomy	6 (35)
Balloon aortic valvotomy	6 (35)
Aortic valve replacement <sup>†</sup>	2 (12)
Subaortic fibromuscular shelf resection	4 (24)
Closure patent arterial duct	3 (18)
Closure atrial septum defect	1 (6)
Age at pulmonary autograft procedure (years)**	23.6 ± 6.9
Age at inclusion (years)**	33.8 ± 6.3
Future child wish	16 (94)
Cardiologist disapproval of pregnancy	3 (18)
History of infertility	2 (12)
Miscarriage	1 (6)
Therapeutic abortion	1 (6)
Completed pregnancies	18
Completed pregnancy after pulmonary autograft procedure	10

\*Values are median (range).

\*\*Values are mean ± SD.

Values in parentheses are percentages.

<sup>+</sup>Not mutually exclusive

<sup>†</sup>One mechanical valve; one bioprosthesis.

for normally distributed continuous variables. Medians and ranges were computed for continuous variables with non-normal distribution.

## Results

The characteristics of the 17 women with pulmonary autograft valve replacement for congenital aortic valve disease enrolled in the study are summarized in Table I.

Five women had 12 pregnancies after the Ross procedure, including one spontaneous (<12 weeks) miscarriage and one elective abortion. The elective abortion was performed at 8 weeks' gestation and was due to the perceived maternal risk associated with the pulmonary autograft.

The complications encountered during the remaining 10 completed pregnancies are detailed in Table II. The mean maternal age at pregnancy was 29.6 ± 4.4 years. The mean interval between the Ross procedure and pregnancy was 5.0 ± 2.8 years (range: 1 to 9 years). Moderate aortic regurgitation was present in three women before pregnancy. Left ventricular systolic function was normal in all women. One woman was in NYHA functional class II before pregnancy, but all oth-

Table II: Overview of complications during 10 completed pregnancies in women after pulmonary autograft valve replacement.

Patient	Pregnancy number	Duration of gestation (weeks)	Birth weight (g)	Complication(s)		
				Cardiac	Obstetric	Perinatal
A	1	37	3,280	0	CS	0
	2	39	3,185	0	CS	0
B	2	38	3,530	0	0	0
	3	38	3,340	0	0	0
C	4	37	3,150	NYHA	0	0
	3	39	2,730	0	0	SGA
D	4	29	1,400	0	PL, PA, CS, PPH	PD
	1	35	1,700	0	PL, V	PD, SGA
E	2	29	700	0	PPROM, PL	PD, SGA, PM
	1	40	4,100	NYHA	PIH	0

CS: Emergency Cesarean delivery; NYHA: NYHA class deterioration during pregnancy; PA: Placental abruption; PD: Premature delivery; PIH: Pregnancy-induced hypertension; PL: Premature labor; PM: Perinatal mortality; PPH: Postpartum hemorrhage; PPROM: Preterm premature rupture of membranes; SGA: Small for gestational age; V: Vacuum-assisted delivery.

ers were in class I. None of the women received anti-coagulants or other cardiac medication.

Two women experienced a temporary deterioration of NYHA class (from class I to II) during pregnancy; however, no drug therapy was started and both women recovered after pregnancy. No episodes of syncope, arrhythmia, angina, thromboembolism, or endocarditis occurred during pregnancy.

Serious obstetric and neonatal complications were observed during two pregnancies. Patient C, who was known to have a protein S deficiency, was admitted to hospital at 26 weeks' gestation due to vaginal blood loss during her second pregnancy. Placental abruption was suspected and an emergency Cesarean delivery at 29 weeks' gestation was performed. The abruption diagnosis was confirmed. The delivery was further complicated by postpartum hemorrhage which required additional blood transfusion. The baby (a male, body weight 1,400 g) was admitted to the neonatal intensive care unit for respiratory distress.

At 18 weeks into her second pregnancy, patient D's membranes ruptured prematurely, and despite efforts to prolong the pregnancy this led to a premature delivery. At 29 weeks a male baby (body weight 700 g) was delivered, but died shortly after birth. No post-mortem examination was performed.

Additional complications observed included: Cesarean delivery (n = 2, for protraction of the second stage of labor); vacuum delivery (n = 1); pregnancy-induced hypertension (n = 1); premature labor leading to premature delivery (n = 1); and small for gestational age (n = 2). At a mean follow up of 5.5 ± 2.6 years all surviving children were in general good health. No recurrence of congenital heart disease was recorded.

Eight of 17 women (47%) were childless, the primary

reasons being advanced age (n = 3), expected health risks associated with maternal cardiac status (n = 2), socioeconomic situation (n = 2), and inheritance risk of congenital heart disease (n = 1). Two of these women were discouraged from becoming pregnant on cardiological grounds, although both were contemplating pregnancy.

The reported median age at menarche was 13 years (range: 10 to 17 years), with primary amenorrhea occurring in one woman. Eight women began taking oral contraceptives at an early age; hence, information on the patient's menstrual cycle was gathered for the remaining nine women. The median duration of the natural menstruation cycle was 30 days (range: 28 to 45 days), indicating the presence of oligomenorrhea (n = 1). Additional reported menstrual cycle disorders were dysmenorrhea (n = 2), menorrhagia (n = 1), and secondary amenorrhea (n = 1, for nine months) (not mutually exclusive). Two other women reported primary female infertility, but both became pregnant after hormonal substitution therapy. Note: It must be realized that the above-mentioned menstrual cycle disorders are more related to the underlying congenital aortic valve disease than to the Ross procedure, which was performed at an older age.

During a mean follow up of 10.2 ± 3.9 years after the Ross procedure (all 17 women), two women required a reintervention for structural valve deterioration. One woman (no previous pregnancy) developed a severe stenosis of the pulmonary autograft and underwent balloon valvotomy at 12 years after the Ross procedure. The valvotomy was unsuccessful and subsequently a homograft was implanted. Another woman developed complications of both the autograft in the aortic position and the homograft in the pulmonic

Table III: Maternal and fetal outcome of pregnancies in women with congenital aortic valve disease with (Dore and Somerville and current series) and without (Silverside) pulmonary autograft valve replacement.

Series	Completed pregnancies (n)	Birth weight (g)	Complication(s)		
			Cardiac	Obstetric	Perinatal
Dore and Somerville (11)	14	3,200	HF (1)	CS (4)	PM (1)
Current series	10	2,712	NYHA (2)	CS (3), PL (3), PA (1), PPRM (1), PIH (1), V (1)	PD (3), SGA (3), PM (1)
Total	24	2,997	NYHA (2), HF (1)	CS (7), PL (3), PA (1), PPRM (1), PIH (1), V (1)	PD (3), SGA (3), PM (2)
Silverside et al. (16)*	49	-	HF (2), AA (1)	PPH (1)	PD (5), SGA (1)

AA: Atrial arrhythmia; HF: Heart failure. Other abbreviations as Table II.

\*This study did not focus on obstetric complications; thus, the number of obstetric complications may be underestimated.

position, consisting of moderate aortic regurgitation in combination with a severe pulmonary regurgitation. Right atrial and ventricular enlargements were also documented. At nine years after the Ross procedure (five years after her last pregnancy) the pulmonary autograft was replaced by a composite aortic repair (Bentall procedure) and a new homograft placed in the pulmonic position.

## Discussion

The key finding of the present case series was that women with pulmonary autograft valve replacement for aortic valve disease can successfully carry pregnancy to term. Nevertheless, serious non-cardiac complications must be taken into account. Furthermore, whilst age at menarche and menstrual cycle were relatively normal, a few women reported menstrual cycle disorders (possibly related to the underlying congenital aortic valve disease, rather than to the Ross procedure). Finally, almost all women had or wished to have children in the future, illustrating the importance of pregnancy research.

Pregnancy in woman with severe congenital aortic stenosis is associated with an increased risk of cardiac complications (15,16). Prophylactic valve replacement is recommended in young women with severe aortic stenosis contemplating pregnancy, in order to avoid future problems (10). The implantation of a mechanical heart valve leads to the requirement of oral anticoagulants, which in turn increases the risk of embryopathy and stillbirth (2). In contrast, bioprosthetic valves have

a significantly higher incidence of valve failure than mechanical valves. A natural history study of 232 young women with prosthetic valves showed that the 10-year rates of valve loss with bioprosthetic, mechanical, and homograft valves were 82%, 29%, and 28%, respectively (6). Furthermore, earlier studies have suggested an accelerated deterioration of bioprosthetic valves during or shortly after pregnancy (3,4), although other more recent studies failed to confirm this finding (5-7). The pulmonary autograft procedure has been recommended by some groups as an attractive alternative for AVR in young women contemplating pregnancy, as it is associated with low thrombogenicity and longer valve durability (10,11). A long-term follow up study investigating the outcome of the Ross procedure showed survival rates of 85% and 60% at 10 and 20 years, respectively, and freedom from any reoperation of 76% and 62%, respectively (17). A recent study conducted by Yacoub et al., investigating 264 Ross patients operated on at Harefield, UK, or at Erasmus MC, The Netherlands, demonstrated an even better outcome, with a 10-year survival rate of 95.4% and freedom from autograft reoperation of 94.9% at 10 years (18). Unfortunately, only limited data are available on the durability of pulmonary autografts in pregnant women. No evidence of valve deterioration was indicated in one report of 14 pregnancies in eight women, amongst whom right-sided obstruction occurred in two cases at nine and 15 years after the pulmonary autograft valve replacement (at 4 and 7 years after a second pregnancy) (11). The remaining patients were free of valve deterioration, with a mean

follow up of 16.5 years. In the present study with a mean follow up of 10.2 years after the Ross procedure, two women required reoperation for structural valve deterioration at nine and 12 years, respectively, after the Ross procedure.

A summary of the available literature on pregnancy and pulmonary autograft procedure (11), together with data from the present series, is presented in Table III. These data were compared to the largest series of pregnancies in patients with congenital aortic stenosis without pulmonary autograft (16). The five pregnancies in women with a pulmonary autograft in the prospective study by Siu et al were not included in the summary, as no specific pregnancy data were presented (15). Overall, serious cardiac complications were rare, and only one case of heart failure was described by Dore and Somerville (11). This woman suffered heart failure, probably due to a dilated cardiomyopathy that was unrelated to aortic or pulmonary valve dysfunction. These authors concluded that this might have been related to myocardial damage after several cardiac operations (11). Most women (88%) in the present series had undergone previous cardiovascular surgery, though none had developed cardiomyopathy during pregnancy.

Remarkably, when combining data from both series, perinatal mortality was extremely high (two of 24 pregnancies). No perinatal mortality was encountered in the series of Silversides et al., who investigated pregnancies in patients with congenital aortic stenosis (16). Perinatal mortality in developed countries is an extremely rare complication, occurring in <0.8% of the pregnancies in the general population of The Netherlands (19). The infant described by Dore and Somerville (11) died on the ninth day due to spina bifida and hydrocephalus. In the present series, preterm premature rupture of the membranes leading to preterm delivery was the main cause of perinatal death.

Premature delivery is a well-known cause of infant morbidity and mortality, which was illustrated by this case. In addition, there was an overall increased rate of premature deliveries and children born as small-for-gestational age. This may be related to a reduced placental perfusion secondary to endothelial dysfunction in women known to have congenital aortic valve disease. Endothelial dysfunction is associated with increased pressor sensitivity, activation of the coagulation cascade, and a loss of vascular integrity, all of which are responsible for a decreased perfusion of the microvasculature (20).

Among the present patients, menarche occurred at approximately 13 years, which was comparable to the period of 12.8 years reported in the general population. Delayed menarche (>16 years) with normal secondary

sexual development found in one woman was suggestive of primary amenorrhea. In the guidelines of the Dutch College of General Practitioners (NHG), it is reported that <5% of menarche occurs in patients after the age of 16 years. Furthermore, two women who reported infertility became pregnant after hormonal substitution therapy.

### Study limitations

Within the present study, it was important to note several potential limitations. First, the retrospective study design necessitated a review of the patients' medical records, and, consequently missing values were inevitable. Second, a selection bias may have been introduced because only survivors were included. Third, the lack of a control group limited the possibility of performing solid comparisons. Fourth, only those women were included who underwent the Ross procedure for congenital aortic valve disease; hence, these data should not be extrapolated to women undergoing such surgery for other reasons. Finally, given the small sample size, all conclusions of the present study must be regarded with caution.

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