CONGENITAL HEART DISEASE

Non-cardiac complications during pregnancy in women with isolated congenital pulmonary valvar stenosis

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Background: Information on the outcome of pregnancy in patients with pulmonary valvar stenosis is scarce, mostly limited to cardiac complications observed during pregnancy.
Objectives: To investigate the magnitude and determinants of non-cardiac and fetal risks during pregnancy of women with isolated pulmonary valvar stenosis.
Methods: Using the nationwide registry (CONgenital CORvitia), 106 women with (un-)corrected pulmonary valvar stenosis receiving care in six tertiary medical centres in The Netherlands were included. A total of 51 women had 108 pregnancies, including 21 (19%) miscarriages and 6 elective abortions.
Results: In the 81 completed (>20 weeks of gestation) pregnancies, we observed a high number of hypertension-related disorders (n = 12, 15%, including pre-eclampsia (n = 4) and eclampsia (n = 2)), premature deliveries (n = 14, 17%, including one twin) and thromboembolic events (n = 3, 3.7%). Furthermore, recurrence of congenital heart defects in the offspring was detected in three children (3.7%, pulmonary valvar stenosis (n = 2) and complete transposition of the great arteries in combination with anencephaly). In addition to the intrauterine fetal demise of the transposition child, three other children died shortly after birth owing to immaturity, hydrocephalus combined with prematurity and meningitis (overall offspring mortality, 4.8%).
Conclusion: In this largest report on pregnancy in women with (un-) corrected isolated pulmonary valvar stenosis, an excessive number of (serious) non-cardiac complications and mortality were observed in the offspring.

Isolated congenital pulmonary valvar stenosis is a relatively rare (2%) congenital heart disease (CHD), which is found in approximately 4.6–7.0/10 000 live births.[1 2] Typically, pulmonary valvar stenosis is characterised by a bifoliate (20%) or trifoliate valve, with varying degrees of fusion of the commissures and fibrous thickening.[3] Depending on the severity of the obstruction, the clinical presentation ranges from asymptomatic, with excellent long-term survival, to early development of severe right-ventricular failure that may even lead to death when left uncorrected.[4] Nowadays, the long-term (up to 30 years) prognosis of patients with severe pulmonary valvar stenosis surgically corrected or treated with balloon valvoplasty is also excellent, although at the cost of pulmonary regurgitation and the possible need for re-intervention.[5–7] Most patients with pulmonary valvar stenosis will reach childbearing age in relatively good health.

It is generally assumed that female patients with pulmonary valvar stenosis, even when severe, can expect a normal pregnancy and delivery. Interestingly, reports published thus far have focused on the occurrence of cardiac complications.[8–13] Detailed recordings of the non-cardiac and neonatal complications, however, are scarce.

Our study aimed to identify the magnitude and determinants of (non-) cardiac and fetal risks during pregnancy of women with pulmonary valvar stenosis, including the recurrence of risk of CHD in the offspring.

METHODS

Using the CONgenital CORvitia registry, a nationwide database that registers patients with CHD receiving care in all tertiary (and most secondary) medical centres in The Netherlands, we were able to identify 119 patients with isolated pulmonary valvar stenosis (aged 18–45 years) who are seen at the outpatient clinics of tertiary medical centres. Of these 119 patients, 106 (89%) provided informed consent for this study. The identified cohort therefore represents most patients with pulmonary valvar stenosis receiving care in the six major tertiary medical centres in The Netherlands. The institutional review board or ethics committee at each participating centre approved the protocol before patient inclusion.[14–16]

Questionnaires were used only as a check for completeness of the available data from medical records. Baseline data included: previous surgical procedures, comorbidity and medical history using the European Paediatric Cardiac Coding; age at inclusion; medication; fertility (infertility: >2 years of pregnancy attempts and documented by gynaecologist); miscarriages (spontaneous fetal loss before 20 weeks of gestation) and elective abortions.

Detailed information of each completed (>20 weeks of gestation) pregnancy was recorded (when applicable prepartum, peripartum and postpartum values): parity status; mode of delivery; use of cigarettes, alcohol, drugs or medication; physical examination (including blood pressure and heart rate), and 12-lead and 24-h electrocardiographic (Holter) registrations. Transthoracic echocardiographic assessment of right and left ventricular systolic function;

Abbreviations: CHD, congenital heart disease; PIH, pregnancy-induced hypertension

Table 1 Baseline characteristics of the patient population with congenital pulmonary valvar stenosis

Characteristics	Total population	Childless population	Population with completed pregnancy
Number of patients	106	60	46
Mean (SD) age at inclusion (years)	29.4 (6.7)	26.2 (4.2)	33.6 (7.1)
Patients with repair	68 (64.2%)	41 (68.3%)	27 (58.7%)
Open valvulotomy	54 (50.9%)	31 (51.6%)	23 (50.0%)
Balloon dilatation	14 (13.2%)	10 (16.7%)	4 (8.7%)
Associated cardiac defect			
Atrial septal defect	21 (19.8%)	13 (21.7%)	8 (17.4%)
Number of abortions			
Spontaneous	21	1	20
Elective	6	2	4

dimensions of both atria and ventricles; pulsed wave colour and Doppler quantification of pulmonary valvar stenosis (none, mild (15–50 mm Hg), moderate (50–80 mm Hg) and severe (>80 mm Hg)) and the severity of pulmonary valvar regurgitation (none, mild, moderate and severe) were recorded when available. Although echocardiograms were recorded in all patients, only those that were adequate to quantitatively assess pulmonary valvar stenosis and regurgitation and were recorded within 2 years of pregnancy were used.

Documented complications in medical records were grouped into general, cardiac, obstetric and neonatal events.

- *General pregnancy complications*: Pregnancy-induced hypertension (PIH; new-onset hypertension, blood pressure >140 mm Hg systolic or >90 mm Hg diastolic without proteinuria after 20 weeks of gestation), pre-eclampsia (PIH with >0.3 g proteinuria in 24-h urine sample), eclampsia (pre-eclampsia with grand mal seizures), haemolysis elevated liver enzymes low platelets syndrome, infections requiring antibiotic treatment, stroke, thromboembolic complication or gestational diabetes.
- *Cardiac complications*: Symptomatic heart failure or arrhythmic events (according to the attending cardiologist) requiring treatment, New York Heart Association functional class deterioration (⩾1 class, developed during pregnancy and persists >1 year postpartum), myocardial infarction, endocarditis or cardiac death.
- *Obstetric interventions/complications*: Assisted vaginal (forceps/vacuum) or caesarean delivery; premature rupture of membranes (rupture of membranes before the onset of uterine contractions); prolongation of second stage of delivery (nullipara >2 h, multipara >1 h); premature labour (labour at <37 weeks gestation); postpartum haemorrhage requiring transfusion (vaginal delivery >500 ml, caesarean section >1000 ml) documented by a gynaecologist requiring transfusion.
- *Neonatal complications*: Premature birth (delivery at <37 weeks of gestation); small-for-gestational-age birth weight (<10th centile); fetal demise (intrauterine death at ⩾20 weeks of gestation); neonatal death (within the first year after birth) or recurrence of congenital heart disease.

Statistical analysis

A Clintrial data entry program was used to record information and was converted to SPSS (V.11.0) for statistical analysis. Descriptive statistics for nominal data, depending on context per pregnancy or patient, were expressed in absolute numbers and percentages. After checking for normality, mean values and standard deviations (SDs) were calculated for normally distributed continuous variables; non-normal distributed continuous variables are presented as median with quartiles. A comparison of baseline characteristics (parity, use of cigarettes/alcohol, medication, New York Heart Association class, repair, presence of right-ventricular hypertrophy, qualitative pulmonary valvar stenosis and pulmonary regurgitation severity) and occurrence of the above-mentioned cardiac, general pregnancy, obstetric and neonatal complications was made using the χ^2 test or Fisher's exact test. Outcome rates were analysed by logistic regression with random effects with Gaussian distribution (STATA V.8.0), considering that patients represent clusters of pregnancies and the dependence of pregnancies with respect to outcome within the same patient. This last statistical method corrects for multiple pregnancies in a single patient also known as within-patient correlation.

Clinical outcome data were compared with known incidences of normal pregnancies in the Western world.

RESULTS

Table 1 summarises the baseline characteristics of the 106 enrolled female patients with isolated congenital pulmonary valvar stenosis.

Sixty patients were childless at inclusion; 48 (80%) of them wish to have children in the future. Table 2 depicts the most important reasons for the patients being childless.

A total of 108 pregnancies (between 1 January 1985 and 2005) were observed in 51 patients, including five subfertile patients who became pregnant after treatment (n = 5, including hormonal substitution therapy, intrauterine insemination and in vitro fertilisation) or spontaneously (n = 1). Four additional gestations that had not reached term at the time of analysis were excluded. There were 81 completed

Table 2 Patients' primary reason for being childless

	n = 60
Age (mostly too young)	22
Social (education, occupation and no partner)	20
No desire to have children	5
Attempt to get pregnant or pregnant at time of analysis	4
Assumed risk of complications related to PS	4
Mental retardation	3
Genetic counselling*	2

PS, pulmonary valvar stenosis.
*Ehlers Danlos and Noonan syndrome.

pregnancies, 21 miscarriages (19.4%, 17 patients, one remained childless), and 6 elective abortions (5 patients, of which 2 remained childless). Most (n = 19) miscarriages occurred early (<12 weeks) and most remained unexplained except for two miscarriages where the father was diagnosed with balanced translocation of chromosome 13 and 14, also known as Roberts' disease.

The complications occurring during these completed pregnancies are the study's primary interest. Table 3 shows the baseline characteristics per completed pregnancy (n = 81, 46 women). The appendix describes the cardiac, general, obstetric and neonatal complications per patient.

General complications

All-cause hospitalisation during pregnancy prior to delivery was recorded in 17 (21%, 20 admissions) of the 81 completed pregnancies; most occurred during the third trimester (median 30 weeks). The most important reasons for admission were hypertensive disorders (n = 6), premature labour (n = 4) and vaginal bleeding (n = 4). Twelve (14.6%) pregnancies were complicated by hypertensive disorders. PIH was observed in 6 (7.4%), pre-eclampsia in 4 (4.9%) and eclampsia in 2 (2.5%), including one patient who also developed haemolysis, elevated liver enzymes, low platelets syndrome. Three (3.7%) thromboembolic complications were observed. In two patients deep venous thrombosis was diagnosed and in another patient a pulmonary embolus was suspected, but owing to pregnancy this could not be confirmed. All three patients received low-molecular weight-heparin treatment. Furthermore, infections requiring antibiotic treatment (n = 15, mainly genitourinary tract infections, including one patient with postpartum endometritis), anaemia treated with iron supplements prescribed by doctors (n = 4) and gestational diabetes (n = 3) were documented. No cerebrovascular accidents or transient ischaemic attacks were reported.

Table 3 Baseline characteristics per completed pregnancy in women with congenital pulmonary valvar stenosis

	n = 81
Mean (SD) maternal age at pregnancy (years)	28.4 (4.7)
Parity status at pregnancy	
Primiparous	45 (55.5%)
Multiparous	36 (44.5%)
Use of cigarettes during pregnancy	10 (12.3%)
Use of alcohol during pregnancy	5 (6.2%)
Cardiac drugs continued during pregnancy	8 (9.9%)
Physical examination	
Mean (SD) SBP (mm Hg)	126 (19)
Mean (SD) DBP (mm Hg)	76 (10)
NYHA class before pregnancy	
Class I	72 (88.9%)
Class II	9 (11.1%)
PS severity (within 2 years) before pregnancy	
None	15 (18.5%)
Trivial/minor	48 (59.3%)
Moderate	6 (7.4%)
Severe	1 (1.2%)
Unknown	11 (16.0%)
PR severity (within 2 years) before pregnancy	
None	25 (30.9%)
Trivial/minor	30 (37.0%)
Moderate	12 (14.8%)
Severe	2 (2.5%)
Unknown	12 (14.8%)
Right ventricular dilatation present at pregnancy	12 (14.8%)

DBP, diastolic blood pressure; NYHA, New York Heart Association; PR, pulmonary regurgitation; PS, pulmonary valvar stenosis; SBP, systolic blood pressure.

Cardiac complications

In only two pregnancies, the observed temporary worsening of New York Heart Association class (class I>II) persisted for >1 year postpartum. Palpitations and problems of arrhythmias were reported in nine pregnancies; however, their cardiologists did not initiate investigation of the arrhythmias. No changes in pulmonary valvar function were detected during follow-up of pregnancy in any of the patients. No episode of syncope, endocarditis, angina pectoris or myocardial infarction was recorded.

Obstetric interventions or complications

Eight primary caesarean sections were attributed to prior caesareans (n = 4), eclamptic seizures, abruptio placentae, a prolapsed umbilical cord and intrauterine growth restriction (all n = 1). The remaining 74 vaginal births needed help for several reasons, including induction of labour (n = 14, 17.2%), vacuum delivery (n = 7, 8.6%) and use of forceps (n = 2, 2.5%). Prolongation of the first stage of labour (n = 1), fetal distress (n = 1, decelerations on cardiotocography) and vacuum delivery failure (n = 1) were the reasons for three secondary caesarean sections. Other observed obstetric complications were postpartum haemorrhage (n = 13, 16.0%), premature rupture of membranes (n = 5, 6.2%) and prolongation of second stage of delivery (n = 4, 4.9%).

Neonatal complications

Of the 82 children, 13 (16.0%; including one twin) were born prematurely after a median of 34 (range 23–36) weeks of gestation. Nine (11.1%) children were small for gestational age, including only one child in the prematurely born group. CHD in the offspring was diagnosed in three children: pulmonary valvar stenosis (n = 2) and transposition of the great arteries (n = 1). The child with a complete transposition of the great arteries also had anencephaly; this combination resulted in intrauterine fetal demise at 23 weeks of gestation. Three other children died shortly after birth owing to immaturity, hydrocephalus combined with prematurity and meningitis.

Our efforts to identify baseline patient characteristics that could predict the occurrence of pregnancy complications were unsuccessful. The association that showed a trend towards significance after correction for within-patient correlation was the relationship between correction for pulmonary valvar stenosis and the occurrence of premature delivery (p = 0.072). No other associations with the baseline characteristics and outcome rates were found in this population.

DISCUSSION

In this the largest reported series so far, we describe 108 pregnancies in 51 patients with (un-) corrected isolated pulmonary valvar stenosis, including 21 miscarriages and 6 elective abortions. We observed a higher than expected number of serious pregnancy/obstetric (eg, hypertension-related disorders, miscarriages, thromboembolic complications and premature rupture of membranes) and neonatal (eg, premature delivery and offspring mortality) complications.

Hypertension-related disorders are normally seen in approximately 8% of all pregnancies, but in the present series we found these disorders in 12 (14.8%) completed gestations.[17] Remarkably, in addition to four pregnancies complicated by pre-eclampsia, two other patients experienced eclamptic seizures. Eclampsia is normally a rare condition with a reported incidence in the developed countries of 4–5 cases/10 000 livebirths and is generally associated with

substantial maternal and neonatal morbidity. Despite the fact that in this study the mothers and their offspring survived the ordeal without sequelae, this finding demands further investigation.[18 19] During 7 of the 12 pregnancies the women were nulliparous, a well-known risk factor of hypertension-related disorders. The percentage of nulliparous women found in the study cohort, however, did not exceed that of the general population. Three episodes occurred in women with a positive history of pregnancy-related hypertension. None of the patients were teenagers or >35 years at the time of pregnancy. None of the patients had chronic hypertension, renal disease, antiphospholipid antibody syndrome, vascular or connective tissue disease, or thrombophilia at the time of pregnancy or inclusion. No fetal-related known risk factors were documented. Overall, only two reports of pulmonary valvar stenosis pregnancy (38 patients) recorded hypertension-related disorders (see Methods); both studies report a case of pregnancy-related hypertension: pre-eclampsia (n = 1) and pregnancy-induced hypertension (n = 1).[9 11] Several mechanisms, either solitary or combined, may be hypothesised. Firstly, activation of neurohormonal pathways in patients with CHD may alter vascular remodelling associated with pregnancy-induced hypertension and (pre-) eclampsia. Secondly, endothelial dysfunction is present in patients with CHD. Finally, oxidative stress may interact with the pathophysiological mechanisms behind pregnancy-induced hypertension and (pre-) eclampsia.

The observed rate of miscarriages (19.4%) is slightly higher than the 13% expected in the general population in The Netherlands and contrasts with the lower miscarriage rates reported in earlier series.[11 12] The review by McAnulty *et al*[20] showed a miscarriage rate of 20% in patients with pulmonary valvar stenosis, which supports our observations. It needs to be taken into account that miscarriage pregnancies are difficult to investigate in a retrospective setting, especially owing to the lack of postmortem examinations. In addition, the increased health awareness of patients with CHD may lead to an overpresentation of miscarriages. In comparison with healthy women, women with CHD are more likely to take a pregnancy test at an early stage, whereas women in good health will consider these early miscarriages to be delayed menstruation cycles.

During pregnancy and in the postpartum period, patients are at risk for thromboembolic complications due to the presence of all three components of Virchow's triad: venous stasis, endothelial injury and a hypercoagulable state. Nevertheless, the incidence of thromboembolic events is normally 1/1000–2000 pregnancies.[21 22] We recorded three venous thromboembolic complications in 81 pregnancies. All three events occurred in patients with corrected pulmonary valvar stenosis and none of them had comorbidity that could explain the events—for example, inherited thrombophilia, malignancy, systemic disease, recent surgery or trauma, disease needing hormonal replacement therapy or bone marrow diseases. None of the patients smoked. Other risk factors, including a pacemaker and advised bed rest, may have had a role. In our opinion, prophylactic treatment is sensible in patients at high risk for thromboembolic events, including immobilised patients. Further research, however, is necessary to confirm our findings.

The observed preterm birth rate (16%) is also higher than that generally reported in the industrialised world (10%) and exceeds prestudy expectations as only a few isolated cases were previously reported.[8–10 13 23] Of the 13 premature deliveries, 6 occurred spontaneously. Urinary tract infections, maternal smoking and polyhydramnion may have had a role in these spontaneous preterm deliveries. The remaining seven premature births were due to gynaecological intervention. The reasons for intervention were eclampsia, maternal cardiac disease, twin pregnancy, suspected umbilical cord prolapse, fetal congenital anomaly, intrauterine growth restriction and socioeconomic reasons (all n = 1). Early detection and prevention of treatable causes—for example, (urinary tract) infections and encouraging patients to stop smoking—can potentially decrease the number of preterm births.[24–26] The importance of decreasing premature birth rate can be illustrated by the associated mortality in the offspring (see later). In two children who died, prematurity or immaturity had an important role.

Premature rupture of the membranes is an important instigator of premature labour and delivery responsible for 30–40% of preterm deliveries in the general population. In our study, the premature rupture of membranes was documented in 2 of the 13 premature deliveries.[24]

Recurrence risk of CHD was found in 3.7%, which is in agreement with the 3.5% found in the literature, but exceeding the occurrence of 0.5% found in the general population.[12 27–30] The presence of a complete transposition of the great arteries had a minor role in the fetal demise, as the child's prognosis was already limited due to the presence of anencephaly. Together with infant mortality (n = 3), the overall offspring mortality was 4.9%, which is normally <1% in the general population in the Western world. Three of the four deaths were associated with premature delivery; although the numbers are still small, we may speculate that premature delivery is important. Early detection and prevention of premature delivery seems to be essential in reducing the high offspring mortality.

Limitations

Firstly, the retrospective design necessitated a review of the patient's medical records, consequently leading to missing values. Nevertheless, all mentioned complications had to be documented by medically qualified personnel in the records according to the preset definitions before data entry. Additional medical records were examined when cardiology records did not provide sufficient information. In particular, the obtained echographical data should be interpreted with caution, because of bias introduced by the ample missing data. On the other hand, reporting echographical data that are >2 years would also be clinically incorrect, as changes are expected over time. Secondly, the availability of parameters of ventricular or valvular functioning was limited to the level of qualitative estimations. Thirdly, selection bias could be introduced by excluding miscarriage or abortion pregnancies. However, these pregnancies are difficult to investigate in a retrospective setting, especially owing to the lack of postmortem examinations. Furthermore, these pregnancies cannot develop complications associated with the second and third trimesters (eg, pre-eclampsia; also, cardiac complications are unlikely in this early stage of pregnancy with its limited volume load); therefore, including these pregnancies would underestimate these risks. Hence, all conclusions of this study must be drawn with caution.

CONCLUSION

Several non-cardiac complications are common during gestation in women with (un-) corrected isolated pulmonary valvar stenosis. In particular, the incidence of hypertension-related disorders, preterm delivery and offspring mortality are high. In counselling women with isolated pulmonary valvar stenosis before pregnancy, early detection and dealing with risk factors for hypertension-related disorders and premature birth are essential to improve pregnancy outcome.

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APPENDIX

Table Overview of pregnancies with complications in women with congenital pulmonary valve stenosis

Patient	Pregnancy	Corrected	Cardiac complications	General complications	Obstetric complications/ interventions	Neonatal complications
A	I	–			F	
B	I	–	NYHA		CS	
	II	–	NYHA		CS, PPH	
	III	–	NYHA	INF	CS	
	IV	–	NYHA		CS‡	
C	I	–		INF	V	
D	I	–		P	PL, V, PPH	PD
E	II	–	NYHA			
F	I	–		GDM, P	PSD	
G	I	–	NYHA	INF, AN	CS‡	
	II	–	NYHA†	INF, AN	CS	
H	I	–		PIH		SGA
	II	–		PIH		
I	II	–		INF		
	III	–		PPH		SGA
J	I	–		P		
K	I	–				CHD
	II	–	NYHA	P		
L	I	–		E	PL	PD
M	I	–	NYHA		PSD, PPH	
	II	–	NYHA	INF, GDM		
N	I	–				CHD, SGA
	II	–				SGA
O	I	–				NM
P	I	–				SGA
Q	II	+			PROM	
R	I	+		PIH	PROM	
S	I	+	NYHA	INF	PL, V	PD
	II	+	NYHA		PL	PD
T	I	+		VAG	PL	PD, NM
U	I	+			PPH	
	II	+		INF	PROM, PL, PPH	PD
	III	+			PPH	
V	I	+	NYHA		PL	PD, SGA, NM
	II	+		INF	PROM, PL, CS	PD
W	I	+	NYHA	E, HELLP	CS	PD
X	I	+			PL	
	II	+		GDM	F	
Y	I	+	NYHA		PL	PD
Z	I	+	NYHA	INF, AN		
AA	I	+		INF		SGA
BB	I	+		VAG		
CC	I	+			CS	PD
	II	+	NYHA	VAG		
	III	+			V	
DD	I	+			PPH	
EE	I	+			Abruptio placentae, CS	
FF	I	+		PIH	PPH	
	II	+		PIH		
	III	+		INF, PIH,VAG	PPH	
GG	I	+	NYHA	INF*	PPH	
HH	II	+			PROM	SGA
II	I	+	NYHA	TEC		
JJ	I	+	NYHA			
	II	+	NYHA			
KK	I	+	NYHA†	INF	PSD, V, PPH	
LL	I	+				PD, CHD, FM
	II	+	NYHA	INF		
MM	I	+			V	
NN	III	+		TEC		SGA
	IV	+			PL	PD
OO	I	+		TEC		
PP	I	+		AN	PSD, V, CS‡, PPH	

AN, anaemia; CHD, congenital heart disease in offspring; CS, caesarean section (‡secondary); E, eclampsia; F, forceps assisted delivery; FM, fetal mortality; HELLP, haemolysis elevated liver enzymes low platelets syndrome; INF, infection requiring antibiotics (*postpartum); NM, neonatal mortality; NYHA, New York Heart Association; P, pre-eclampsia; PD, premature delivery; PIH, pregnancy-induced hypertension; PL, premature labour; PPH, postpartum haemorrhage; PROM, premature rupture of membranes; PSD, prolongation of second stage of delivery; SGA, small for gestational age; TEC, thromboembolic complication; V, vacuum-assisted delivery; VAG, antepartum vaginal bleeding.
NYHA, New York Heart Association class deterioration during pregnancy (†persisted postpartum).