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Fertility, Pregnancy and Delivery in Women after Biventricular Repair for Double Outlet Right Ventricle

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Key Words
Congenital heart disease · Pregnancy · Complications

Abstract
Objectives: To investigate outcome of pregnancy and fertility in women with double outlet right ventricle (DORV). ***Methods:*** Using 2 congenital heart disease registries, 21 female patients with DORV (aged 18–39 years) were retrospectively identified. Detailed recordings of each patient and their completed (>20 weeks gestation) pregnancies were recorded. ***Results:*** Overall, 10 patients had 19 pregnancies, including 3 spontaneous miscarriages (16%). During the 16 live birth pregnancies, primarily (serious) noncardiac complications were observed, e.g. premature labor/delivery (n = 7 and n = 3, respectively), small for gestational age (n = 4), preeclampsia (n = 2) and recurrence of congenital heart disease (n = 2). Except for postpartum endocarditis and deterioration of subpulmonary obstruction, only mild cardiac complication pregnancies were recorded. Two women with children reported secondary female infertility. Several menstrual cycle disorders were reported: secondary amenorrhea (n = 4), primary amenorrhea (n = 3) and oligomenorrhea (n = 2). ***Conclusion:*** Successful pregnancy in women with DORV is possible. Primarily noncardiac complications were observed and only few (minor) cardiac complications. Infertility and menstrual cycle disorders appear to be more prevalent.

Introduction

In double outlet right ventricle (DORV), a rare spectrum of congenital heart defects (0.5–1.0%), more than 50% of both great arteries arise from the morphologic right ventricle. Surgical repair primarily depends on the localization/size of the ventricular septal defect and the presence of associated lesions. If feasible, a biventricular repair is preferred. After biventricular repair, the long-term (15-year) survival ranges between 95.8 and 89.5%, i.e. most patients will reach childbearing age [1]. Data on

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Table 1. Description of the 21 patients with biventricular repaired DORV

Patient	Age at inclusion years	Type of DORV based on location of VSD	Associated lesions	Type of repair	Age at biventricular repair, years	Age at menarche years	Contraindication expressed by cardiologist	History of infertility	Miscarriage (M), pregnancy (P)
A	28	Subaortic	Valvar PS	TOF	13	13	No	No	–
B	23	Subaortic	Valvar PS	TOF	1	14	No	No	–
C	22	Subaortic	Valvar PS	TOF	3	18	No	No	–
D	37	Subaortic	Valvar PS	TOF	9	14	No	No	–
E	34	Subaortic	PFO	TOF	4	12	No	No	–
F	23	Subpulmonary	TGA	Tunnel	8	14	Yes	No	M (1)
G	30	Subpulmonary	TGA	Mustard	3	13	No	No	–
H	28	Subpulmonary	Coarctation + AoS/AoR + azygos vein continuation	Tunnel	3	15	No	No	–
I	26	Subpulmonary	TGA	Tunnel	14	13	No	No	–
J	22	Subpulmonary	TGA + valvar PS	Tunnel	8	12	No	No	–
K	24	Subpulmonary	TGA + valvar PS	Tunnel	10	13	No	No	–
L	24	Doubly committed	TGA + PA	Tunnel	7	11	No	No	–
M	39	Subaortic	PV agenesis	TOF	26	15	No	No	P (1)
N	39	Subaortic	Valvar PS	TOF	12	13	No	No	P (1)
O	32	Subaortic	Subvalvar AoS + AoR	TOF	4	14	Yes	No	P (1)
P	30	Subaortic	Infundibular PS	TOF	7	12	Yes	Yes	M (1)[a], P (1)
Q	37	Subaortic	PV agenesis	TOF	9	11	Yes	No	P (7)
R	25	Subpulmonary	TGA	Tunnel	13	13	Yes	No	P (1)
S	36	Subpulmonary	TGA + valvar PS	Tunnel	16	17	No	No	P (1)
T	30	Subpulmonary	TGA	Mustard	5	16	No	Yes	M (1), P (2)
U	30	Doubly committed	CC-TGA + infundibular PS + ASD II + persistent left caval superior vein	Tunnel	10	13	No	No	P (1)[a]

VSD = Ventricular septal defect; PS = pulmonary valve stenosis; TOF = tetralogy of Fallot; PFO = patent foramen ovale; AoS = aortic stenosis; AoR = aortic regurgitation; TGA = complete (D-)transposition of the great arteries; PA = pulmonary atresia; PV = pulmonary valve; CC-TGA = congenitally corrected transposition of the great arteries; ASD II = atrial septal defect type II.

[a] Twin pregnancy.

pregnancy outcome in women with biventricular repaired DORV are scarce [2–7].

The primary objective of the present study was to evaluate the risks associated with pregnancy in women after biventricular repair for DORV. Secondary aims were to assess the prevalence of infertility, the reasons for being childless and the prevalence of menstrual cycle disorders.

Patients and Methods

For the present study, female patients with DORV (aged 18–45 years) were identified using the nationwide Congenital Corvitia (CONCOR) registry funded by the Netherlands Heart Foundation and a Belgian tertiary medical center's adult congenital heart disease (CHD) database. Written informed consent was obtained and the institutional review boards of the 7 participating tertiary medical centers approved the protocol.

The patients' medical history was recorded using the European Paediatric Cardiac Code short list. Information regarding menstrual cycle and fertility was obtained through questionnaires and, when applicable, gynecological files: 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 or more 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 (more than 2 years of pregnancy attempts and documented by gynecologist); miscarriages (spontaneous fetal loss ≤20 weeks) and/or elective abortions.

Detailed information regarding each completed pregnancy was also recorded according to protocol, as described earlier [8, 9]. The Clintrial data management program was used to record data, which were then converted to SPSS (version 11.0). We limited the analyses due to the sample size; only numbers/percentages and, when applicable, median values are presented.

Table 2. Overview of complications during the 16 live birth pregnancies in women with biventricular DORV repair

Patient	Pregnancy	Cardiac complications	General complications	Obstetric complications	Neonatal complications
M	1			PL	PD, CHD[a]
O	1	S	P	Placenta previa, PPH	
P	1	NYHA↓	UTI	PL, V	PD
Q	1			PL, V	
Q	3				CHD[b], SGA
Q	4				SGA
Q	7	SPO, E			
R	1		UTI	F, PL, PSD	SGA
S	1			PL	
T	1	NYHA↓	VAG		SGA
T	2		UTI	PL, PROM, PSD	PD
U	1		P, UTI	PL	
Overall		NYHA↓ (2), E (1), S (1), SPO (1)	UTI (4), P (2), VAG (1)	PL (7), PSD (2), V (2), F (1), Placenta previa (1), PPH (1), PROM (1)	SGA (4), PD (3), CHD (2)

PL = Premature labor; PD = premature delivery; CHD = recurrence of congenital heart disease in the offspring; S = near-syncope; P = preeclampsia; PPH = postpartum hemorrhage; NYHA↓ = NYHA class deterioration during pregnancy; UTI = urinary tract infection; V = vacuum delivery; SGA = small for gestational age; SPO = subpulmonary obstruction; E = endocarditis; F = forceps delivery; PSD = prolonged second stage of delivery; VAG = vaginal bleeding; PROM = premature rupture of membranes.

[a] Velocardiofacial syndrome with ventricular septal defect.

[b] Double-chambered right ventricle with a ventricular septal defect and patent arterial duct.

Results

Twenty-one female patients (median age 30 years) who had undergone biventricular repair for DORV were included (table 1). Overall, 19 pregnancies were documented in 10 different women. Three of these gestations ended in a spontaneous miscarriage (16%). No elective abortions were performed. Complications observed during the 16 completed live birth pregnancies are described below (table 2).

Cardiac Complications

In 2 patients (P and T), temporary NYHA class deterioration during pregnancy was observed. Both patients recovered quickly after delivery. Near syncope during an episode of palpitations was documented in patient O. Follow-up echocardiograms revealed progression of (sub-)pulmonary obstruction with concomitant right ventricular dilatation during patient Q's sixth pregnancy. After delivery, balloon dilatation followed by pulmonary homograft placement was needed. Five months after her seventh pregnancy the same patient was diagnosed as having endocarditis. Blood cultures revealed a monoculture of *Staphylococcus aureus*. Surgical interventions (redo-pulmonary homograft) and antibiotic therapy were necessary. No other cardiac complications were documented.

General Pregnancy Complications

Preeclampsia was suspected in 3 different patients and confirmed in 2 (12.5%). No other hypertension-related disorders, thromboembolic complications, stroke and/or gestational diabetes were documented.

Obstetric Complications

Premature labor occurred during 7 (44%) pregnancies (in 7 different patients) at a median of 32 weeks (range 27–36). In 3 pregnancies (14%), premature delivery could not be avoided. Placenta previa lateralis was the indication for the only primary cesarean section. Other observed obstetric complications were prolongation of the second stage of delivery (n = 2, 10%), premature rupture of membranes (n = 1, 5%) and postpartum hemorrhage (n = 1, 5%).

Neonatal Complications

All 17 children (1 twin, 53% female) were born alive. Four term-born children (24%) of 3 different women were small for gestational age. Recurrence of CHD was found in 2 children. In the first child prenatally diagnosed with velocardiofacial syndrome, fetal echocardiography suggested an isolated ventricular septal defect. Postpartum transthoracic echocardiography confirmed this diagnosis. The other child was diagnosed with double-chambered right ventricle associated with a ventricular septal defect and patent ductus arteriosus. No offspring mortality was reported.

Twelve women were childless at inclusion for age-related reasons (n = 7, too young to start a family), socioeconomic reasons (n = 4, e.g. career or financial situation) and perceived risk of complications (n = 1). No primary infertility was documented. Two patients with children reported secondary infertility, despite hormonal therapy and in vitro fertilization procedures. Reported menstrual cycle disorders were: primary amenorrhea (n = 3, 14%), secondary amenorrhea (n = 4, 19%) and oligomenorrhea (n = 2, 10%).

Discussion

The key finding of the present study is that patients with biventricular repaired DORV can successfully carry pregnancy to term. Nevertheless, mainly (serious) noncardiac complications were observed. Fertility may be diminished. Menstrual cycle disorders were frequently reported.

During pregnancy, only minor cardiovascular complications were encountered. Weight gain and volume loading can result in a decrease in exercise tolerance even in healthy women. Therefore, NYHA class deterioration can be considered a physiological phenomenon when it resolves quickly after delivery. As demonstrated by the development of (sub-)pulmonary obstruction and endocarditis, careful follow-up during pregnancy and after delivery remains necessary.

From an obstetric point of view, the observed premature labor rate is alarming. Its importance is illustrated by the fact that all patients were admitted to hospital and needed medical intervention. Moreover, 3 pregnancies ended in a premature delivery with subsequent offspring morbidity. Siu et al. [2] also reported 1 premature delivery in a patient with repaired DORV.

Important offspring complications included the higher than expected (24 vs. 10%) number of small for gestational age children and the recurrence of CHD. Sawhney et al. [3] also reported that the child of their patient with repaired DORV was small for gestational age. The risk of CHD recurrence appears high, though we need to take into account that a TXB1 gene mutation explained 1 recurrence [10].

Fertility may be compromised as, despite therapeutic intervention, no pregnancy could be achieved in 2 patients reporting secondary infertility. Menstrual cycle disorders, in particular amenorrhea appear to be more prevalent. Primary amenorrhea generally occurs in 0.1–2.5% of the women in the general population. In our patients the incidence was remarkably higher (14%), which may explain higher age at menarche (13.6 versus 13.15 years in the general population) [11]. Identically, the prevalence of secondary amenorrhea was also higher than the 3/1,000 women per year reported in the guidelines of the Dutch College of General Practitioners. Diagnostic tests to pinpoint the cause of primary/secondary amenorrhea, however, were not performed. Therefore, important etiologies (e.g. hypothalamic hypogonadism) cannot be ruled out with confidence.

Several potential limitations must be noted. The retrospective design necessitated a review of patients' medical records and, consequently, missing values are inevitable. Selection bias may have been introduced by the fact that we only included survivors. Within-patient correlation due to the inclusion of 1 patient with 7 pregnancies may have influenced complication rates. Last, given the small sample size, all conclusions of the present study must be drawn with caution.

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References

1 Brown JW, Ruzmetov M, Okada Y, Vijay P, Turrentine MW: Surgical results in patients with double outlet right ventricle: a 20-year experience. Ann Thorac Surg 2001;72:1630–1635.

2 Siu SC, Sermer M, Harrison DA, Grigoriadis E, Liu G, Sorensen S, Smallhorn JF, Farine D, Amankwah KS, Spears JC, Colman JM: Risk and predictors for pregnancy-related complications in women with heart disease. Circulation 1997;96:2789–2794.

3 Sawhney H, Suri V, Vasishta K, Gupta N, Devi K, Grover A: Pregnancy and congenital heart disease – maternal and fetal outcome. Aust N Z J Obstet Gynaecol 1998;38:266–271.

4 Siu SC, Sermer M, Colman JM, Alvarez AN, Mercier LA, Morton BC, Kells CM, Bergin ML, Kiess MC, Marcotte F, Taylor DA, Gordon EP, Spears JC, Tam JW, Amankwah KS, Smallhorn JF, Farine D, Sorensen S: Prospective multicenter study of pregnancy outcomes in women with heart disease. Circulation 2001;104:515–521.

5 Kaemmerer H, Bauer U, Stein JI, Lemp S, Bartmus D, Hoffmann A, Niesert S, Osmers R, Fratz S, Rossa S, Lange PE, Beitzke A, Schneider KT, Hess J: Pregnancy in congenital cardiac disease: an increasing challenge for cardiologists and obstetricians – a prospective multicenter study. Z Kardiol 2003;92:16–23.

6 Presbitero P, Somerville J, Stone S, Aruta E, Spiegelhalter D, Rabajoli F: Pregnancy in cyanotic congenital heart disease: outcome of mother and fetus. Circulation 1994;89:2673–2676.

7 Whittemore R, Hobbins JC, Engle MA: Pregnancy and its outcome in women with and without surgical treatment of congenital heart disease. Am J Cardiol 1982;50:641–651.

8 Drenthen W, Pieper PG, Ploeg M, Voors AA, Roos-Hesselink JW, Mulder BJ, Vliegen HW, Sollie KM, Ebels T, van Veldhuisen DJ: Risk of complications during pregnancy after Senning or Mustard (atrial) repair of complete transposition of the great arteries. Eur Heart J 2005;26:2588–2595.

9 Drenthen W, Pieper PG, van der Tuuk K, Roos-Hesselink JW, Voors AA, Mostert B, Mulder BJ, Moons P, Ebels T, van Veldhuisen DJ: Cardiac complications relating to pregnancy and recurrence of disease in the offspring of women with atrioventricular septal defects. Eur Heart J 2005;26:2581–2587.

10 Yagi H, Furutani Y, Hamada H, Sasaki T, Asakawa S, Minoshima S, Ichida F, Joo K, Kimura M, Imamura S, Kamatani N, Momma K, Takao A, Nakazawa M, Shimizu N, Matsuoka R: Role of TBX1 in human del22q11.2 syndrome. Lancet 2003;362:1366–1373.

11 Fredriks AM, Van Buuren S, Burgmeijer RJ, et al: Continuing positive secular growth change in the Netherlands. Pediatr Res 2000;47:316–322.