CONGENITAL HEART DISEASE

Pregnancy and delivery in women after Fontan palliation

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Objectives: To evaluate the outcome of pregnancy in women after Fontan palliation and to assess the occurrence of infertility and menstrual cycle disorders.
Design and patients: Two congenital heart disease registries were used to investigate 38 female patients who had undergone Fontan palliation (aged 18–45 years): atriopulmonary anastomosis (n = 23), atrioventricular connection (n = 5) and total cavopulmonary connection (n = 10).
Results: Six women had 10 pregnancies, including five miscarriages (50%) and one aborted ectopic pregnancy. During the remaining four live-birth pregnancies clinically significant complications were encountered: New York Heart Association class deterioration; atrial fibrillation; gestational hypertension; premature rupture of membranes; premature delivery; fetal growth retardation and neonatal death. Four of seven women who had attempted to become pregnant reported female infertility: non-specified secondary infertility (n = 2), uterus bicornis (n = 1) and related to endometriosis (n = 1). Moreover, several important menstrual cycle disorders were documented. In particular, the incidence of primary amenorrhoea was high (n = 15, 40%), which resulted in a significant increase in age at menarche (14.6 (SD 2.1) years, $p < 0.0001$, compared with the general population).
Conclusion: Women can successfully complete pregnancy after adequate Fontan palliation without important long-term sequelae, although it is often complicated by clinically significant (non-)cardiac events. In addition, subfertility or infertility and menstrual disorders were common.

In 1971, Fontan, Baudet and Keutzer established the use of the single ventricle in tricuspid atresia to generate systemic blood flow, while allowing pulmonary blood to flow directly from the right atrium to the pulmonary artery without an (adequate) interposed ventricle.[1] Since then, although initial results were disappointing, modifications of Fontan palliation have improved long-term survival of (functional) single ventricles and complex malformations considered unsuitable for biventricular repair. Despite serious long-term sequelae, such as impaired systemic ventricular function and systemic atrioventricular valve regurgitation, patients have reached and will reach childbearing age in the decades to come.[2]

Pregnancy itself encompasses several important haemodynamic changes (for example, increased cardiac output and reduced systemic vascular resistance) that may potentially threaten the health of both the mother with a Fontan circulation and her offspring. In particular, the surplus of systemic venous return may lead to complications, such as atrial arrhythmias, oedema and ascites. On the basis of the available literature, mostly ''successful'' case reports and one larger clinical study, the pre-existent routine tendency to discourage pregnancy was abandoned.[3] The presence of long-term sequelae after Fontan palliation and the need for drugs (for example, oral anticoagulation) were suggested as pregnancy risk indicators.[3–5]

Additionally, it has been hypothesised that exposure to chronic hypoxaemia before and chronic venous congestion after this palliation may influence ovarian function with subsequent menstrual cycle disorders and sub- or infertility. Data on the menstrual cycle and fertility in women after Fontan operation, however, are limited.[6]

The primary objective of the present study was to identify the magnitude and determinants of pregnancy risks in a contemporary Fontan palliated population including the outcome in the offspring. Secondary objectives were to investigate whether menstrual cycle is disturbed and fertility compromised.

PATIENTS AND METHODS

For the present study, female patients after Fontan palliation aged 21–58 years were identified in the nationwide CONCOR (CONgenital CORvitia) registry funded by the Netherlands Heart Foundation and a Belgian tertiary medical centre's adult congenital heart disease database. Overall, the ongoing registries had included 7486 patients. The institutional review board or ethics committee at each of the six participating tertiary centres approved the protocol.[7 8] Overall, 44 women were identified, two of whom had died of non-pregnancy related causes. Of the contacted 42 patients, 38 provided written informed consent (participation rate 90%).

Medical records served as the basis for data collections. Questionnaires were used only to supplement the available data from medical records (mainly information on menstrual cycle), and complications had to be registered in medical files by qualified personnel. Baseline data were basic anatomy, prior surgical procedures, invasive catheter measurements after Fontan, co-morbidity and medical history recorded according to the European Paediatric Cardiac Coding; age at inclusion; age at menarche; menstruation cycle (duration, regularity without hormonal substitution); primary amenorrhoea (menarche not established at 16th birthday, in the presence of normal growth and secondary sexual development); secondary amenorrhoea (absence of menstruation for

Abbreviations: CONCOR, CONgenital CORvitia; CS, caesarean section; NYHA, New York Heart Association; TCPC, total cavopulmonary connection

180 days or more after menarche in the absence of pregnancy, lactation or menopause); oligomenorrhoea (menstrual bleeding at intervals > 35 days), polymenorrhoea (menstrual bleeding at intervals < 24 days); menorrhagia (excessive or prolonged (> 7 days) menstrual bleeding occurring at regular intervals characterised by loss of blood clots or development of anaemia); infertility (more than two years of pregnancy attempts, investigated and documented by a gynaecologist); miscarriages (spontaneous fetal loss before 20 weeks of gestation); and elective abortions.

Detailed information concerning each completed (> 20 weeks of gestation) pregnancy was recorded (when applicable prepartum, peripartum and postpartum data): mode of delivery; parity status; use of cigarettes, alcohol or illicit drugs; drug prescriptions; New York Heart Association (NYHA) functional class; physical examination (including blood pressure and heart rate); 12-lead ECG; transthoracic echocardiograms (qualitative systemic ventricular systolic function, qualitative systemic atrioventricular valve regurgitation) and 24 h ECG (Holter) recordings.

Documented complications were divided into cardiac, general, obstetric and neonatal complications. Cardiac complications were symptomatic documented arrhythmia or heart failure requiring treatment (according to an attending cardiologist), myocardial infarction, protein-losing enteropathy, and endocarditis. General complications were pregnancy-induced hypertension (occurring after ⩾ 20 weeks of gestation, > 140 mm Hg systolic or 90 mm Hg diastolic without proteinuria); pre-eclampsia (pregnancy-induced hypertension with > 0.3 g of proteinuria/24 h urine sample); eclampsia (pre-eclampsia with grand mal seizures); haemolysis, raised liver enzymes, low platelets syndrome; thromboembolic complications; gestational diabetes; and stroke. Obstetric complications were assisted (forceps, vacuum or caesarean section (CS)) delivery; premature rupture of membranes (membrane rupture before the onset of uterine contractions); prolonged second stage of delivery (nullipara > 2 h, multipara > 1 h); premature labour (spontaneous onset of labour at < 37 weeks of gestation); and postpartum haemorrhage (vaginal delivery > 500 ml, CS > 1000 ml documented by a gynaecologist and requiring transfusion). Neonatal complications were premature delivery (delivery at < 37 weeks of gestation); small for gestational age birth weight (< 10th centile); fetal death (intrauterine death at ⩾ 20 weeks of gestation); neonatal death (death within the first month after birth); and recurrence of congenital heart disease.

Information recorded on a Clintrial data entry program was converted to SPSS V.11.0 (SPSS Inc, Chicago, Illinois, USA) for statistical analysis. Descriptive statistics for nominal data were expressed as absolute numbers and percentages. Means (SD) were calculated for normally distributed continuous variables after checking for normality. Medians and quartiles were computed for continuous variables with non-normal distribution. A one-sample t test was used to compare age at menarche with the age at menarche in the general population. All tests of the zero hypotheses were two sided. A value of $p < 0.05$ was considered significant.

RESULTS

Overall, we investigated 38 female patients (age at inclusion 28.6 (6.2) years) after definitive Fontan operation (table 1).

Six women had 10 pregnancies (between 1986 and 2003), including five miscarriages and one ectopic pregnancy. A single patient had three of the five miscarriages (patient U; see supplemental table on the *Heart* website—http://www.heartjnl.com/supplemental), all of them before 12 weeks of gestation. The two other miscarriages both developed after 12 weeks of gestation; the first at 20 weeks' gestation was caused by physical abuse by the patients' partner. The attending gynaecologist attributed the other patient's miscarriage at 16 weeks to a non-specified fetal cardiac malformation.

Three women had four live-birth pregnancies (patients V, W and LL; see supplemental table on the *Heart* website—http://www.heartjnl.com/supplemental). Table 2 summarises the complications during these pregnancies.

Complications

Cardiac complications

During both of patient V's pregnancies her exercise tolerance gradually decreased, resulting in an observed third trimester NYHA class deterioration (I > II). After delivery she quickly recovered without residual sequelae. Furthermore, she developed atrial fibrillation (mean ventricular response rate 116 beats/min) at 33 weeks' gestation during her second pregnancy. Chemical cardioversion with flecainide (150 mg) failed. Electrical cardioversion (one shock, 200 J) was successful. A few days after delivery, atrial fibrillation recurred and was resolved by electrical cardioversion (two shocks, 50 and 100 J).

General pregnancy complications

First trimester painless vaginal bleeding during patient V's second pregnancy and gestational hypertension during patient W's first pregnancy were the only documented general complications.

Obstetric complications

Several obstetric events occurred. Patient V's first pregnancy was complicated by premature rupture of membranes (25th week) that led to spontaneous premature labour. Delivery could not be avoided. After failure to deliver the child with forceps and vacuum assistance, it was decided that a secondary CS at 26 weeks of gestation was the only safe option. During her second pregnancy, she was hospitalised again, this time at 28 weeks, due to intrauterine growth retardation. After the patient was hospitalised for seven weeks, she underwent a primary CS for a breech presentation. The first and only child of patient LL was also delivered by elective CS. No complications developed during the three CS deliveries. Patient W's vaginal delivery, however, was complicated by postpartum haemorrhage (estimated blood loss 900 ml).

Neonatal complications

Both children of patient V were born prematurely; her first-born girl delivered at 26 weeks of gestation died two months after delivery due to the complications of meningitis. The two other children, both born at 38 weeks' gestation, were small for their gestational age, weighing 2180 g (W) and 2300 g (LL). Three children were alive and healthy at inclusion (median follow up five years). No other complications were recorded.

Fertility and menstrual cycle disorders

The most important reasons that the remaining 35 women gave for being childless were expected health risks associated with the Fontan circulation (n = 13), age (n = 10), socioeconomic situation (n = 7), infertility (n = 2), and mental retardation (n = 1); two patients were still attempting to get pregnant. Twenty four of these childless patients (69%) had discussed pregnancy with their attending cardiologist. Seventeen of them were discouraged from getting pregnant on cardiological grounds. Nonetheless, 27 of the 35 childless women (77%), including nine women who were advised against pregnancy, reported that they were contemplating pregnancy.

Table 1 Baseline characteristics of the female patients after Fontan repair (n = 38)

Primary cardiac malformation	
Tricuspid atresia	18 (47.4%)
Double inlet left ventricle	7 (18.4%)
Pulmonary atresia with intact ventricular septum	3 (7.9%)
Double outlet right ventricle	3 (7.9%)
Complete AV septal defect	2 (5.3%)
Other	5 (18.5%)
Palliative procedures before Fontan	
Blalock–Taussig shunt	16 (42.1%)
Waterston shunt	3 (7.9%)
Classic Glenn shunt	2 (5.3%)
Rashkind atrioseptostomy	1 (2.6%)
Pulmonary artery banding	1 (2.6%)
None	15 (39.4%)
Median age at first palliation (years)	3.5 (range 1–25)
Type of Fontan repair (at menarche/at inclusion*)	
AP connection (RA-AP)	22 (57.9%)/23 (60.5%)
AV connection (RA-RV)	8 (21.1%)/5 (13.2%)
Total cavopulmonary connection	3 (7.9%)/10 (26.3%)
None	5 (13.2%)/0
Median age at (primary) Fontan repair (years)	7.5 (range 3–25)
Number of repeat Fontan operations	20†
Sequelae at inclusion	
Atrial flutter/atrial fibrillation	19 (50.0%)
Permanent pacemaker	6 (15.7%)
Protein C deficiency	6 (15.7%)
Thromboembolic complications	4 (10.5%)
Protein-losing enteropathy	1 (2.6%)
New York Heart Association class at inclusion	
I/II	36 (94.7%)
III/IV	2 (5.3%)
Echocardiography at inclusion	
Severe impairment of systemic ventricular function	5 (13.2%)
Severe (grade III–IV) systemic AV valve regurgitation	6 (15.7%)

*These may differ from the type at menarche due to repeat Fontan procedures; †including three third operations.
AP, atriopulmonary; AV, atrioventricular; RA, right atrial; RV, right ventricular.

Four of the seven women who attempted to get pregnant reported female infertility. In two patients, the gynaecological investigations found a probable cause: uterus bicornis with a rudimentary right horn in addition to bilateral ovarian cysts (patient P); and endometriosis (patient BB; see supplemental table on the *Heart* website—http://www.heartjnl.com/supplemental). Both consulted their cardiologist before going ahead with infertility therapy. When confronted with these patients' plans their physicians discouraged pregnancy. The patients followed their doctor's orders, although patient BB had the ''unplanned'' ectopic pregnancy abortion mentioned above. Gynaecologists also investigated suspected subfertility or infertility in two other women (patients U and V; see supplemental table on the *Heart* website—http://www.heartjnl.com/supplemental); however, the diagnosis was not definitive. Subsequent hormone therapy and in vitro fertilisation procedures remained unsuccessful, and the two established gestations terminated spontaneously. Nevertheless, spontaneous pregnancies resulted in two live-birth pregnancies (patient V) and a third consecutive miscarriage (patient U; see above).

Table 2 Overview of complications during live-birth pregnancies in women after Fontan palliation

Patient	Pregnancy number	Complications			
		Cardiac	General	Obstetric	Neonatal
V	1	NYHA ↓		PROM, PL, F, V, CS	PD, ND
	2	NYHA ↓, AFL/AF	VAG	CS	PD
W	1		PIH	PPH	SGA
LL	1			CS	SGA

AF, atrial fibrillation; AFL, atrial flutter; CS, caesarean section; F, forceps delivery; ND, neonatal death; NYHA ↓, New York Heart Association class deterioration during pregnancy; PD, premature delivery; PIH, pregnancy-induced hypertension; PL, premature labour; PPH, postpartum haemorrhage; PROM, premature rupture of membranes; SGA, small for gestational age; V, vacuum delivery; VAG, vaginal bleeding.

Reported age at menarche was on average 14.6 (2.1) years, which is significantly higher ($p < 0.001$) than the 13.0–13.2 years found in the general population in The Netherlands and Belgium. The incidence of primary amenorrhoea was particularly high (n = 15, 40%). Because 17 women started taking oral contraception at an early age, information on patients' menstrual cycles was gathered on the remaining 21 patients. The median duration of the natural menstruation cycle was 28 days, ranging between 21–42 days, indicating the presence of polymenorrhoea (n = 1) and oligomenorrhoea (n = 2). Additional reported menstrual cycle disorders were menorrhagia (n = 3) and secondary amenorrhoea (n = 3, one probably due to hypothyroidism, range of amenorrhoea duration 1–12 years).

DISCUSSION

Women with adequate Fontan palliation can become pregnant without clinically significant long-term sequelae, although they may have clinically significant complications. Fertility appears to be diminished. In addition, menstrual cycle disorders in women after Fontan repair were common. Particularly, delayed menarche due to a high incidence of primary amenorrhoea and the high prevalence of secondary amenorrhoea are striking.

Putting the reported pregnancy complications into the overall perspective highlights several findings (table 3[3 5 9–23]).

Arrhythmias are well-known long-term sequelae after Fontan palliation. Patients who have had atriopulmonary connection and atrioventricular connection Fontan operations are especially prone to develop supraventricular arrhythmias due to right atrial tissue exposure to higher

Table 3 Overview of the literature on pregnancy after Fontan repair according to the definitions and overall results of the present study

Article (reference)	Patients (no)	Completed pregnancies	Miscarriage/ abortion	Cardiac complications	Pregnancy complications	Obstetric complications	Neonatal complications
Girod[9]	1	1	–	–	–	PL (1)	PD (1), SGA (1)
Hess[10]	1	1	–	SVT (1)*	–	PL (1)	PD (1), ND (1)
Carmona[11]	1	1	–	–	–	–	–
Gerardin[12]	1	1	–	SVT (1), HF (1)	PIH (1)	PL (1), F (1)	PD (1)
Carp[13]	2	2	1/–	AFL/AF (1)	–	CS (1), PROM (1), PPH (1)	PD (2), SGA (1)
Cohen[14]	1	1	–	AFL/AF (1)	–	PROM (1), PL (1)	PD (1), ND (1)
Osmers,[15] Braun[16]	1	1	–	–	VAG (1)	CS (1)	PD (1)
Lao[17]	1	1	–	–	VAG (1)	PROM (1), PL (1), PPH (1)	PD (1)
Canobbio,[3] Fyfe,[18] Mair[19]	21	15	13/5	SVT (1), HF (1), NYHA ↓ (1)	–	CS (11), PROM (1), PL (1)	CHD† (1), PD (1)
Grunwald[20]	1	1	–	–	–	PPH (1)	SGA (1)
Hoare[5]	3	4	5/2	AFL/AF (2), NYHA ↓ (1)	–	CS (2), PROM (1), PL (1)	PD (4)
Siu[21 22]	5	5	–	AFL/AF (2), NYHA ↓ (2)	–	–	–
Ito[23]	1	1	–	–	–	CS (1)	SGA (1)
Present study	38	4	5/1	AFL/AF (1), NYHA ↓ (2)	VAG (1), PIH (1)	CS (3), F (1), PL (1), PROM (1), PPH (1), V (1)	PD (2), SGA (2), ND (1)
Overall	78	39	24/8	AFL/AF (7), NYHA ↓ (6), SVT (3) HF (2)	VAG (3), PIH (2)	CS (19), PL (8), PROM (6), PPH (4), F (2)	PD (15), SGA (5), ND (3), CHD† (1)

*No treatment initiated during pregnancy; †atrial septal defect.
AF, atrial fibrillation; AFL, atrial flutter; CHD, congenital heart disease; CS, caesarean section; F, forceps delivery; HF, heart failure; ND, neonatal death; NYHA ↓, New York Heart Association class deterioration; PD, premature delivery; PIH, pregnancy-induced hypertension; PL, premature labour; PPH, postpartum haemorrhage; PROM, premature rupture of membranes; SGA, small for gestational age; SVT, supraventricular tachycardia, V, vacuum delivery; VAG, vaginal bleeding.

than normal pressures and incisional scar tissue formation. Review of the literature indicates that the type of Fontan palliation may also have an important role in arrhythmias during pregnancy. Women after Fontan palliation developed supraventricular arrhythmias during 26% of the gestations. Interestingly, eight of the 10 patients reported in the literature who developed arrhythmias were known to have non-total cavopulmonary connection (TCPC) Fontan. During pregnancy, the additional circulatory burden, specifically the extra volume load and the enhanced adrenergic receptor excitability mediated by oestrogens and progesterone, can trigger the development of supraventricular arrhythmias in patients with non-TCPC Fontan.[24] NYHA deterioration was also a common cardiac complication (15%), although relatively benign. In accordance with the literature, the deterioration that developed during two of our four reported completed pregnancies was mild and resolved quickly after delivery.

In addition to patient V's episode of painless antepartum bleeding, two other case reports mention the occurrence of antepartum bleeding.[15 17] Importantly, no relationship was found with the anticoagulants used or clotting disorders in any of the reported cases. Pregnancy-induced hypertension is a relatively benign condition when it does not present before the third trimester and is not accompanied by signs of pre-eclampsia. In accordance with these conclusion drawn by Sibai *et al*,[25] no severe maternal or neonatal events developed in the present (second) reported case of gestational hypertension during pregnancy in a patient with Fontan palliation.[11]

Obstetric complications also appear to be a major problem of pregnancy in the context of Fontan palliation (table 3). Intriguingly, including the first pregnancy of patient V, premature rupture of membranes complicated six of the 39 described completed Fontan pregnancies. All ruptures occurred before 37 weeks of gestation, also known as preterm premature rupture of membranes, which is normally seen in only 1.25% of gestations.[26] All but one led to premature labour and subsequent premature delivery (range 26–33 weeks). Taking all reported pregnancies into account, delivery was premature in 15 of the 39 completed pregnancies (39%, range 25–36 weeks). This is extremely high considering that normally the preterm birth rate is 10–12%.[27 28] Moreover, premature delivery is a leading cause of infant morbidity and mortality, illustrated by the fact that all three neonates who were reported to have died (8%) were delivered prematurely.[29] Moreover, almost all prematurely delivered children were admitted to the neonatal intensive care unit for further treatment.

Postpartum haemorrhage, described in the vaginal delivery of patient W, was also reported in other Fontan pregnancies.[13 17 20] Moreover, it was not associated with the use of anticoagulation or the presence of coagulopathies.

Overall, only five children (12.8%, including two in the present study) were small for their gestational age (by definition < 10 centile). In theory, this means that uteroplacental blood flow is sufficient and supports normal fetal growth in most patients with an adequate univentricular circulation. Cardiac malformation was not found in any of the live-born offspring. The fetal cardiac malformation that may have led to the late spontaneous miscarriage could not be confirmed in the medical records. Congenital heart disease recurrence therefore appears to lower in the spectrum (2.6%) than other (complex) congenital heart lesions.

Subfertility or infertility appears to be important, although the number of patients who attempted pregnancy limits statistical analysis. Therapeutic interventions to overcome subfertility or infertility may also carry risks, in particular thromboembolic complications. The spontaneous miscarriage rate also appeared high, as five of the 10 (50%) pregnancies terminated, which is substantially higher than the 34% (24 of 71) reported in the literature and the 10–15% found in the general Western population.

Delayed menarche relative to that of the general Dutch population (14.6 *v* 13.0 years) can be attributed mainly to the high incidence of primary amenorrhoea. Diagnostic tests to

pinpoint the cause of primary amenorrhoea were not performed, therefore important causes (such as hypothalamic hypogonadism and abnormalities of the uterus, cervix or vagina) cannot be ruled out. Age at menarche was also substantially higher than the 13.7 years that Canobbio *et al*[6] reported in patients with Fontan palliation. The prevalence of secondary amenorrhoea (3/38) was also higher than the reported 3/1000 women/year in the guidelines of the Dutch College of General Practitioners. No determinants of these menstrual cycle disorders could be identified.

Several potential limitations must be noted. The retrospective design necessitated a review of patients' medical records, and consequently missing values are inevitable. The inclusion only of survivors may have introduced a selection bias. We limited the literature review to articles with the main body of text in English, German, Dutch or French. This excluded one article.[30] Lastly, given the sample size, all conclusions of the present study must be drawn with caution.

In short, women after Fontan palliation become pregnant with difficulty, as fertility appears to be compromised and complex when accomplished. We believe that the risk of pregnancy is limited for women with Fontan palliation who have adequate repair without significant long-term sequelae, with the most important problem being supraventricular arrhythmias. The high miscarriage rates with their psychological consequences and the frequent occurrence of other clinically significant complications during pregnancy, especially the high incidence of premature labour and delivery and of neonatal death, must, however, be discussed with the patient. In our opinion, these problems are important reasons to regard pregnancy as not advisable. Moreover, long-term consequences of pregnancy in women after Fontan repair cannot yet be foreseen. These remarks, however, need to be restricted to patients with atriopulmonary or atrioventricular connection Fontan, as information on TCPC Fontan is too limited. Meticulous pre-conception analysis is advisable when pregnancy is inevitable. Repeated patient education by qualified medical personnel on the risks of pregnancy and delivery remain important. Larger prospective studies or registries are needed to assess the outcome of pregnancies in patients with congenital heart disease, especially those with complex anomalies.

Supplemental table appears on the *Heart* website—http://www.heartjnl.com/supplemental

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