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Pregnancy Outcomes in Women With Fontan Circulation: A 25-Year Tertiary Care Retrospective Cohort Study of Temporal Trends in Pregnancy

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Abstract

Background

Pregnancy in women with Fontan circulation (FC) is considered high risk, though pregnancy outcomes over time are less well described.

Objectives

The study aimed to describe pregnancy outcomes in patients with FC and evaluate temporal trends over a 25-year period.

Methods

This was a retrospective cohort study of women with FC and documented pregnancy at a tertiary care adult congenital heart disease center (1999-2024) and a comparison of pregnancy outcomes over time (Early Era, 1999-2013; and Contemporary Era, 2014-2024).

Results

Among 21 women (median 27 years, range 19-39) and 46 pregnancies, 25 (54%) resulted in spontaneous abortion (SA), and 21 (46%) live births in 15 women. Median baseline peripheral oxygen saturation (SpO2) was 93% (80%-99%); six women had baseline hypoxia (<90%). Left univentricular morphology was present in 16 (76%) women, right univentricular morphology in five (24%); most (n=18, 86%) had normal ventricular systolic function. Cardiac complications occurred in two (10%) pregnancies (postpartum heart failure, ventricular arrhythmia), with no maternal deaths. Cesarean delivery occurred in 11 (55%), postpartum hemorrhage in three (14%), and preterm birth in 17 (81%), with no neonatal deaths. Pregnancies increased from the Early (n=18) to the Contemporary (n=28) Era (incident rate ratio 2.18, 95% CI 1.21-3.92, p=0.009), though SA, preterm birth, and cesarean delivery were similar. SA was not statistically associated with maternal hypoxia, ventricular morphology/function, anticoagulation, or age, though pregnancy in women with SpO2 <90% never resulted in a term birth.

Conclusions

Pregnancies in patients with FC increased over time, though high rates of SA and preterm delivery persist. Cardiac events occurred in 10%, with no maternal death. These findings support comprehensive preconception counseling, multidisciplinary management, and continued efforts to identify predictors of SA in women with Fontan circulation.

Categories: Cardiology
Keywords: congenital heart disease, fontan circulation, pregnancy, preterm birth, spontaneous abortion

Introduction

Survival for individuals born with single-ventricle congenital heart disease has improved markedly over recent decades, largely due to advances in staged surgical palliation resulting in the Fontan circulation. Contemporary data show that over 80% of patients survive more than 30 years post-Fontan, and this population is expected to grow by 20% in the next decade [1].

Given the success of patients reaching adulthood, there is increased focus and interest in patients with Fontan pursuing pregnancy. Prior studies report increased maternal risk of arrhythmias and heart failure, as well as preterm delivery and increased neonatal mortality [2-7]. According to the modified World Health Organization (mWHO) maternal cardiovascular risk classification, women with uncomplicated Fontan circulation are categorized as mWHO class III, whereas those with complicated Fontan physiology, including ventricular dysfunction, baseline hypoxemia, clinically significant Fontan-associated liver disease or cirrhosis, atrial arrhythmias, or significant valvular disease are considered mWHO class IV [3]. Consequently, guidelines suggest all patients with Fontan circulation should receive care at a center with expertise in pregnancy and heart disease [8]. The majority of the data on pregnancy outcomes in patients with Fontan comes from tertiary care centers [3-6,9] and meta-analyses of such studies [2,7].

Despite the increased survival in patients with Fontan circulation, longitudinal data examining how pregnancy outcomes have evolved over time remain limited [10]. Our tertiary care adult congenital heart disease and cardio-obstetrics program has cared for patients with Fontan circulation achieving pregnancy since 1999, providing a unique opportunity to evaluate maternal cardiac, obstetric, and fetal outcomes across a 25-year period. Accordingly, the objectives of this study were to characterize maternal cardiac, obstetric, and fetal outcomes in pregnancy among women with Fontan circulation and to examine temporal trends in pregnancy outcomes within our cohort.

Materials And Methods

Study design

We performed a single-center retrospective cohort study of women with single-ventricle congenital heart disease post-Fontan palliation, followed by the Columbus Ohio Adult Congenital Heart Disease (COACH) program who experienced pregnancy between the years 1999 and 2024. The Ohio State University's Biomedical Institutional Review Board approved this study with waivered consent (approval number 2023H0313).

Patient identification and data collection

The COACH program has a comprehensive list of patients with Fontan circulation (caring for ~250 individuals with Fontan circulation during the study period), in addition to a detailed record of all cardio-obstetric patients. Using these two lists, we identified and included all patients with a known history of Fontan circulation and a documented pregnancy in the medical record. All documented pregnancies were included in the study irrespective of gestational age and pregnancy outcome. Reported pregnancies without documentation were not included in our study.

Baseline characteristics

Baseline characteristics were collected from the medical record within 12 months of pregnancy, including; maternal race/ethnicity, underlying type of congenital heart disease, single ventricle morphology (univentricular left ventricle (uLV) or univentricular right ventricle (uRV)), age at Fontan completion, Fontan type, comorbid conditions, age at the time of pregnancy, pre-pregnancy body mass index (BMI), pre-pregnancy maternal resting oxygen saturation by pulse oximetry (SpO2), New York heart Association (NYHA) functional class [11], cardiac medications, anticoagulation & antiplatelet medications, and echocardiographic results (with ventricular systolic function categorized as normal, mildly reduced, moderately reduced, or severely reduced based on the report in the medical record).

Outcomes studied

Maternal cardiac outcomes included death (while pregnant or within 42 days of termination of pregnancy) [12], need for cardiac surgery, thromboembolic events (deep venous thrombosis or pulmonary/systemic embolism), heart failure exacerbation (defined as documentation of heart failure, escalation in diuretic therapy, inotrope therapy, or mechanical support), and arrhythmia (defined as sustained atrial arrhythmia and sustained/non sustained ventricular arrhythmia) up to 42 days postpartum.

Maternal obstetric outcomes included mode of delivery (cesarean or vaginal), preeclampsia/eclampsia as documented in the medical record, and postpartum hemorrhage (defined as blood loss >500 mL for vaginal delivery, >1000 mL for cesarean delivery, or need for transfusion due to blood loss) [13]. Cesarean delivery indication was considered obstetric (breech presentation, placental abruption, intrauterine growth restriction, fetal intolerance of labor, and maternal preference for repeat cesarean section) or cardiac (hemodynamic instability including acutely decompensated heart failure and maternal shock).

Fetal outcomes included spontaneous abortion (pregnancy loss prior to viability), stillbirth (fetal death >24 weeks gestation), neonatal death (death within 30 days of birth), live birth, preterm birth (defined by the World Health Organization as birth at <37 weeks gestational age), low birthweight (<2500 grams) [14], and neonatal intensive care admission.

Select pregnancy outcomes were separated into the Early Era (1999-2013) and Contemporary Era (2014-

2024). Outcomes included number of pregnancies, live births, spontaneous abortions, median maternal age, median gestational age, maternal baseline oxygen saturation, ventricular morphology, pregnancies in patients with baseline hypoxia, preterm live births, utilization of invasive hemodynamic monitoring during delivery, and use of aspirin and/or anticoagulation during pregnancy.

Statistical analysis

Categorical data are presented as frequencies and percentages and were compared using chi-square. If there were fewer than five cases per group, Fisher's exact test was used. Continuous variables are presented as median (range) unless otherwise indicated, with normality assessed by the Shapiro-Wilk test. Differences in normally and non-normally distributed variables were assessed using an unpaired two-tailed t-test or Mann-Whitney test, respectively. A multivariable logistic regression model was fitted to evaluate predictors of spontaneous abortion. Covariates were chosen a priori based on prior literature, including hypoxia (defined as systemic saturation <90%, a clinically established threshold for significant cyanosis which has been used previously in patients with Fontan) [15], univentricular morphology (right vs left) and systolic function, use of anticoagulation, and maternal age. A mixed-effects logistic regression model was fitted to account for multiple pregnancies in an individual. Due to the low intraclass correlation coefficient of the mixed-effects model, and thus negligible clustering at the individual level, a standard logistic regression model was chosen. Pregnancies between the two eras were compared using a two-sample Poisson rate test, with the rate defined as the total number of pregnancies divided by the number of years in each period (Early Era, 14 years; Contemporary Era, 10 years). P values ⩽0.050 were considered statistically significant. Analysis was performed using R version 4.4.2 (R Core Team (2024), Vienna, Austria).

Results

Baseline characteristics

In a cohort of 21 female patients with Fontan circulation, there were 46 documented pregnancies; these resulted in 21 live births to 15 patients (four patients had > one live birth; a maximum of three live births to one patient). The median age at the time of pregnancy was 27 years (range 19-39), and median pre-pregnancy BMI was 24 kg/m² (range 19-40). The majority of patients (n = 18 (86%)) self-identified as non-Hispanic White, with three (14%) non-Hispanic Black. Among the 21 women in the cohort, five (24%) had prior atrial arrhythmias and two (10%) had prior documented clinical heart failure. The median baseline oxygen saturation documented within the 12 months preceding pregnancy was 93% (range 80%-99%), with six patients <90% (Table *1*).

Characteristic	Value (N=21)
Age at pregnancy (years)	27 (16-39)
Oxygen saturation (SpO2 %)	93 (80-99)
Maternal race	
Non-Hispanic White	18 (86)
Non-Hispanic Black	3 (14)
Congenital heart disease	
Univentricular right ventricle morphology	5 (24)
DORV	5
Univentricular left ventricle morphology	16 (76)
Tricuspid atresia	10
Double inlet left ventricle	2
PA/IVS	2
PA/VSD	1
PA/AVSD	1
Fontan Data	
Age at Fontan (years)	3 (1.5-19)
Fontan fenestration	12 (57)
Lateral tunnel	11 (52)

Extracardiac	7 (33)
Atrio-pulmonary/classic	1 (5)
Kawashima	2 (10)
Pre Pregnancy Comorbidities	
Atrial arrhythmias	5 (24)
Clinical heart failure	2 (10)
Hypertension	5 (24)
Diabetes	0 (0)
Chronic kidney disease	1 (5)
Obesity	7 (33)
Fontan associated liver disease	17 (80)
Anxiety / depression	10 (48)
Tobacco use	2 (10)
Pre-pregnancy laboratory data	
Serum creatinine (mg/dL)	0.7 (0.5-1.6)
Total bilirubin (mg/dL)	0.8 (0.5-2.5)
Hemoglobin (g/dL)	14.3 (10.9-16.2)
Platelets (K/uL)	196 (100-250)
Pre Pregnancy Medications	
Beta blocker	8 (38)
Diuretic	6 (29)
ACE inhibitor or ARB	6 (29)
Digoxin	2 (10)
Aspirin	10 (48)
Therapeutic anticoagulation	7 (33)
Ventricular systolic function by echocardiography	
Normal	18 (86)
Mildly reduced	2 (10)
Moderately reduced	1 (5)

TABLE 1: Pre-pregnancy Baseline Characteristics

Continuous variables, median (range); Categorical variables, n (%); N = number of women in the study. ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; AV = atrioventricular valve; AVSD = atrioventricular septal defect; DORV = double outlet left ventricle; PA = pulmonary atresia; IVS = intact ventricular septum; VSD = ventricular septal defect; SpO2 = peripheral oxygen saturation.

Single-ventricle morphology was predominantly uLV (n = 16 (76%)), with the most common diagnosis being tricuspid atresia in 10 patients. The five (24%) patients with univentricular right ventricle (uRV) were all due to double outlet right ventricle. Univentricular systolic function by echocardiography was normal in 18 (86%) patients, mildly reduced in two (10%), and moderately reduced in one (5%); none had severely reduced systolic function (Table *1*). Only two (10%) patients had more than mild atrioventricular valve regurgitation (both moderate). The median age at the time of Fontan was three years, with lateral tunnel Fontan in 11 (52%) patients, extracardiac in seven (33%), atrio-pulmonary/classic Fontan in one (5%), and Kawashima in

two (10%). A Fontan fenestration was present in 12 (57%) patients.

The NYHA functional class within 12 months preceding pregnancy was documented for 33 of the 46 pregnancies. Among pregnancies with available data, 26 (79%) occurred in women categorized at NYHA class I, five (15%) in women categorized at NYHA class II, and two (6%) in women categorized as NYHA class III.

Prior to pregnancy, 10 (48%) patients were prescribed antiplatelet therapy (all aspirin, 81 mg) and seven (33%) were prescribed therapeutic anticoagulation (warfarin, n=6; rivaroxaban, n=1), and four (19%) were on neither anticoagulation nor antiplatelet therapy. Other pre-pregnancy medications are outlined in Table *1*.

During all 46 pregnancies, aspirin alone was used in 22 (48%) pregnancies and anticoagulation alone was prescribed in seven (15%) pregnancies, all with low molecular weight heparin (LMWH), while both aspirin and anticoagulation were prescribed in 12 (26%) pregnancies (LMWH = 11, warfarin = 1). Only five (11%) pregnancies were managed on neither aspirin nor anticoagulation. Among the 21 pregnancies that resulted in a liveborn neonate, aspirin alone was used in seven (33%), anticoagulation alone was prescribed in two (9.5%) (all LMWH), and six (29%) were prescribed both aspirin and anticoagulation (all LMWH). A total of six (29%) pregnancies resulting in a liveborn neonate involved no aspirin or anticoagulation. Antiplatelet and anticoagulation status during pregnancy is further outlined in Table *2*.

	All Pregnancies (n=46)	Pregnancies Resulting in Live Birth (n=21)
ASA alone	22 (48%)	7 (33%)
Anticoagulation alone[a]	7 (15%)	2 (9%)
ASA + anticoagulation	12[b] (26%)	6[a] (29%)
No ASA or anticoagulation	5 (11%)	6 (29%)

TABLE 2: ASA and Anticoagulation Status During Pregnancy

ASA = aspirin; LMWH = low molecular weight heparin

[a] All LMWH; [b] 11 pregnancies with LMWH and 1 with warfarin.

Maternal cardiac outcomes

There were no maternal deaths, no cardiac surgeries, and no thromboembolic events during pregnancy or within 42 days postpartum. Arrhythmia in the form of non-sustained ventricular tachycardia occurred in 1 (5%) patient (with double inlet left ventricle) on mobile cardiac telemetry at 38 weeks and 2 days gestation, which prompted delivery at 38 weeks and 6 days. Heart failure occurred in one (5%) patient (with tricuspid atresia) who experienced postpartum hemorrhage requiring transfusion for hemodynamic support, precipitating acute heart failure secondary to volume overload. Additional details of patients who had a live birth are provided in Table *3*.

Patients With a Live Birth	Type of CHD	Total Pregnancies	Total Spontaneous Abortion	Age at Live Birth (years)	Univentricular Function	Pre-pregnancy SpO2	Anticoagulation & Antiplatelet During Pregnancy
1	TA	2	1	26	Normal	94%	No
2	PA IVS	1	0	27	Normal	88%	No
3	PA IVS	5	2	22, 24, 28	Normal	91%	LMWH, ASA[a]
4	TA	1	0	27	Normal	Unknown	No
5	TA	2	1	37	Normal	82%	LMWH
6	TA	1	0	33	Normal	97%	ASA
7	DORV	3	2	23	Normal	90%	ASA
8	TA	1	0	21	Mildly reduced	94%	LMWH
9	TA	5	2	26, 29, 39	Normal	97%	LMWH, ASA[b]
10	PA VSD	3	1	26, 27	Normal	88%	ASA[c]
11	DILV	2	1	24	Normal	96%	ASA
12	DORV	1	0	26	Normal	91%	LMWH, ASA
13	PA, AVSD	2	0	29, 31	Normal	94%	No[d]
14	TA	2	1	30	Normal	97%	No
15	DORV	4	3	27	Normal	94%	LMWH, ASA

TABLE 3: Maternal Characteristics of 15 Patients Accounting for 21 Live Births

ASA = aspirin; AVSD = atrioventricular septal defect; CHD = congenital heart disease; DORV = double outlet right ventricle; DILV = double inlet left ventricle; LMWH = low molecular weight heparin; PA = pulmonary atresia; HT = heart transplant; IVS = intact ventricular septum; SpO2 = peripheral oxygen saturation; TA = tricuspid atresia; VSD = ventricular septal defect

[a] ASA alone, 1 pregnancy/live birth, ASA + LMWH, 2 pregnancies/live births.

[b] ASA alone, 1 pregnancy/live birth, ASA + LMWH, 2 pregnancies/live births.

[c] ASA alone, 2 pregnancies/live births.

[d] No ASA or LMWH, 2 pregnancies/live births.

Delivery mode and obstetric outcomes

Delivery data were available for 20 of the 21 live births. Vaginal delivery occurred in nine (45%), and cesarean delivery in 11 (55%), with all cesarean deliveries performed for obstetric indications. Of the patients with a vaginal delivery, seven delivered in the labor and delivery unit and two in the cardiac intensive care unit (one at our institution, another at a local hospital).

Preeclampsia occurred in one patient during one of her two pregnancies, which resulted in a late preterm delivery. Postpartum hemorrhage occurred in three (14%) patients, all of whom were prescribed antiplatelet therapy or anticoagulation; one due to placental abruption requiring cesarean section (patient prescribed LMWH), and the others after vaginal delivery (one prescribed LMWH, one prescribed aspirin). Further obstetric outcomes are reported in Table *4*.

Parameter	n (%)
Maternal Cardiac Outcomes (n=21)	
Maternal death	0 (0)
Need for cardiac surgery	0 (0)
Arrhythmia	1 (5)
Heart failure	1 (5)
Delivery method (n=20)[a]	
Vaginal delivery	9 (45)
Cesarean section	11 (55)
Obstetric Complications (n=21)	
Preeclampsia	1 (5)
Eclampsia	0 (0)
Postpartum Hemorrhage	3 (14)
Fetal Outcomes (n=46)	
Spontaneous abortion	25 (54)
Stillbirth	0 (0)
Neonatal death	0 (0)
Live birth	21 (46)
Live Birth Outcomes (n=21)	
Preterm birth	17 (81)
Birth weight <2500g[b]	9 (75)
Neonatal intensive care admission	10 (48)
Gestational age data for live births (n=21)	
Gestational age at delivery in weeks (median, range)	34 (24-38)
Term (≥37 weeks)	4 (19)
Late preterm (32-36 weeks)	9 (42)
Very preterm (28-31 weeks)	5 (24)
Extreme preterm (<28 weeks)	3 (14)

TABLE 4: Delivery Characteristics, Obstetric Complications, and Fetal Outcomes

[a] Available for 20 of the 21 live births.

[b] Available for 12 of the 21 live births.

Invasive hemodynamic monitoring was performed during eight (38%) deliveries (cesarean, n=5; vaginal delivery, n=3); seven with an arterial line, including one with concomitant central venous pressure monitoring, and one with central venous pressure monitoring only (Table 5). After delivery, eight (38%) patients (of which seven had invasive monitoring) recovered in the cardiac intensive care unit and the remainder on the postpartum unit.

Patient ID[a]	Age at delivery (years)	Invasive monitor	Type of CHD	Ventricular systolic function	SpO2 (%)	Delivery method	Reason for invasive line
1	26	CVC, Arterial line	TA	Normal	94	Cesarean	Cesarean with epidural anesthesia
3	24	CVC	PA, IVS	Normal	91	Cesarean	Cesarean with epidural anesthesia
7	23	Arterial line	DORV	Normal	90	Cesarean	Cesarean with epidural anesthesia
8	21	Arterial line	TA	Mildly reduced	94	Vaginal	Ventricular dysfunction
9	39	Arterial line	TA	Normal	93	Cesarean	Cesarean with general anesthesia
10	27	Arterial line	PA, VSD, TGA	Normal	88	Vaginal	Delivery at non-tertiary care center
12	26	Arterial line	PA, DORV	Normal	91	Vaginal	Complexity of CHD
15	27	Arterial line	DORV	Normal	94	Cesarean	Cesarean with spinal anesthesia

TABLE 5: Summary of Invasive Hemodynamic Monitoring During Delivery (n=8 deliveries)

[a] ID corresponding to a patient with a live birth, as noted in Table 3.

CHD = congenital heart disease; CVC = central venous catheter; DORV = double outlet right ventricle; TGA = transposed great arteries; PA = pulmonary atresia; TA = tricuspid atresia; VSD = ventricular septal defect; IVS = intact ventricular septum; SpO2 = peripheral oxygen saturation

Fetal outcomes

Out of the 46 documented pregnancies, there were 25 (54%) spontaneous abortions, no stillbirths, and no instances of neonatal death. Live births occurred in 21 (46%) pregnancies, of which 17 (81%) were preterm (median gestational age at delivery was 34 (range 24-38) weeks). Birthweight data were available for 12 of the live births, of which nine (75%) were low birth weight. Nearly half of the live-born infants (n=10, 48%) required admission to the neonatal intensive care unit for interventions such as respiratory support, parenteral nutrition, phototherapy, and antibiotic therapy.

As outlined in Figure *1*, on multivariable analysis there was no association between spontaneous abortion and the presence of hypoxia (odds ratio (OR) 1.5, 95% confidence interval (CI) 0.32-7.46), uRV morphology (OR 1.69, 95% CI 0.32-10.39), single ventricle systolic dysfunction (OR 1.28, 95% CI 0.09-32.23), maternal age (OR 0.92, 95% CI 0.8-1.06) or use of anticoagulation during pregnancy (OR 1.07, 95% CI 0.27-4.37). However, of the 10 pregnancies in women with SpO2 <90% at baseline, only four resulted in a liveborn infant (median gestational age 32 (range 27-36) weeks). Additionally, of the pregnancies in the three women with reduced ventricular function, only one resulted in a live birth (34 weeks gestation).

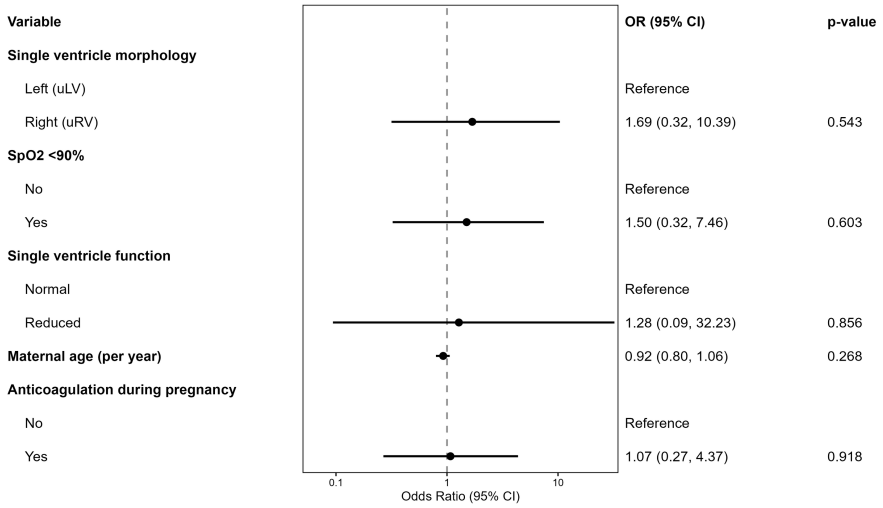


FIGURE 1: Multivariable Logistic Regression Analysis for Predictors of Spontaneous Abortion

uRV = univentricular right ventricle; uLV = univentricular left ventricle; CI = confidence intervals; SpO2 = peripheral oxygen saturation

Outcomes across eras

In comparing maternal characteristics in the Early and Contemporary Eras using a two-sample Poisson rate test, there were significantly more pregnancies in the Contemporary Era (Early Era, n=18; 1.29 pregnancies/year vs Contemporary Era, n=28; 2.80 pregnancies/year (incident rate ratio 2.18, 95% confidence interval 1.21-3.92, p=0.009)) (Figure *2*). Maternal age, SpO2, ventricular morphology, and the number of pregnancies in women with SpO2 <90% were similar (Table *6*). There was a non-significant trend towards increased use of aspirin alone during pregnancy, which did not meet statistical significance (Early Era 5 (29%) vs Contemporary Era 16 (57%), p = 0.084).

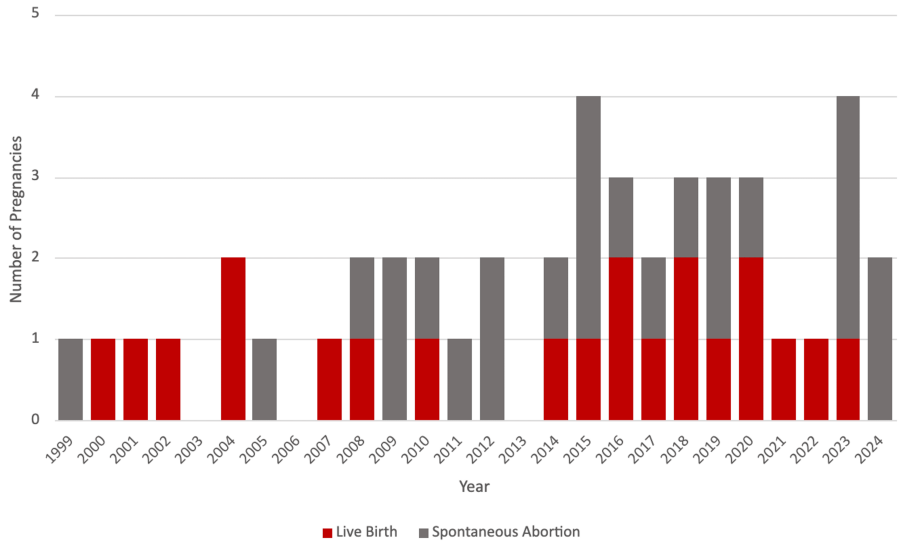


FIGURE 2: Annual Pregnancy Outcomes Among Women with Fontan Circulation (n=46 pregnancies)

Bars represent the number of pregnancies resulting in live birth (red) and spontaneous abortion (gray) each year.

Note: One pregnancy (ending in spontaneous abortion) did not have a definite date (it was before 2010), so it was excluded from this figure.

Pregnancies Per Era	1999-2013 (n=18)	2014-2024 (n=28)	P value	Shapiro-Wilk Test Result (Continuous Variables)	Statistical Test	Test Statistic
Maternal age (years)[c]	26 +/- 6	27 +/- 4	0.306	Normally distributed	Unpaired two-tailed t-test	t=1.036, df=43
Maternal SpO2 (%)[c]	94 (82-99)	93 (80-98)	0.552	Non-normally distributed	Mann-Whitney test	U = 192
Maternal hypoxia (SpO2 <90%)[b]	4 (24)	6 (21)	>0.999	NA	Fisher's exact test	NA
Single ventricle morphology[b]			0.480	NA	Fisher's exact test	NA
Univentricular left ventricle	13 (72)	23 (82)				
Univentricular right ventricle	5 (28)	5 (18)				
Aspirin / Anticoagulation use[a,b]			0.084	NA	Fisher's exact test	NA
Aspirin alone	5 (29)	16 (57)				
Anticoagulation alone	4 (24)	3 (11)				
Aspirin + anticoagulation	4 (24)	8 (29)				
No aspirin or anticoagulation	4 (24)	1 (4)				
Pregnancy outcome[b]			>0.999	NA	Fisher's exact test	NA
Spontaneous abortion	10 (56)	15 (53)				
Live births	8 (44)	13 (46)				
Preterm (live births)[b]	8 (100)	9 (69)	0.131	NA	Fisher's exact test	NA
Gestational age of live births (weeks)[c]	30 +/- 4	33 +/- 4	0.079	Normally distributed.	Unpaired two-tailed t-test	t=1.876, df=17
Delivery method[a,b]				NA	Fisher's exact test	NA
Vaginal	3 (43)	6 (46)	>0.999			
Cesarean	4 (57)	7 (54)				
Invasive monitoring (deliveries)[b]	1 (13)	7 (54)	0.085	NA	Fisher's exact test	NA

TABLE 6: Pregnancy Outcomes by Era

[a] Not available in 1 pregnancy, 1999-2013.

[b] Categorical variables presented as frequencies (%).

[c] Continuous variables are presented as median (range), with normality assessed by the Shapiro-Wilk test. Differences in normally and non-normally distributed variables were assessed using an unpaired two-tailed t-test or Mann-Whitney test, respectively.

Test statistics are reported for t-tests and Mann-Whitney U tests; test statistics are not applicable (NA) for Fisher's exact tests.

Pregnancy outcomes were similar between the two eras, though there were no patients in the Early Era 1 who had a term birth (Table 6). There was a trend towards higher gestational age for live births in the

Contemporary Era, which did not meet statistical significance (median gestational age for Early Era 29 weeks vs Contemporary Era 34 weeks, p = 0.079). Cesarean deliveries were performed at similar frequency, though there was a non-significant increase in the use of invasive monitoring during delivery in the Contemporary Era (1 delivery (13%) vs 7 deliveries (54%), p = 0.085).

Discussion

The outcomes of pregnancy in this cohort of women with Fontan circulation followed at a tertiary care adult congenital heart disease center were notable for maternal cardiac complications in two (10%) patients, delivery by cesarean section in more than half, preterm birth in 81%, and postpartum hemorrhage in 14% (Figure *3*). Thus, adverse events, while not universal, remain clinically significant. Notably, spontaneous abortion occurred in 54% of pregnancies and exceeded the number of live births across the study period. Although spontaneous abortion was not statistically associated with maternal hypoxia, it is notable that none of the women with hypoxia achieved a term pregnancy. These findings reinforce the complexity of pregnancy in individuals with Fontan circulation and the need for preconception counseling and multidisciplinary cardio-obstetric care.

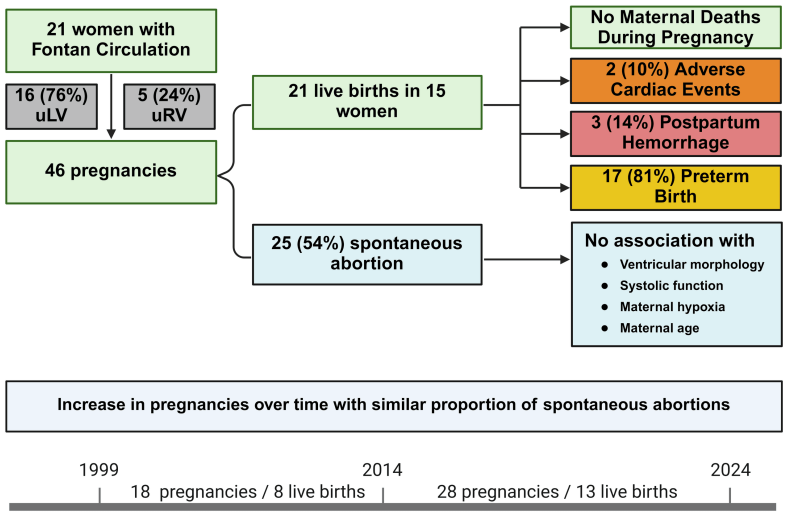


FIGURE 3: Pregnancy Outcomes in Women with Fontan Circulation in Present Study

uRV = univentricular right ventricle; uLV = univentricular left ventricle.

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A large multicenter study reported 3% thromboembolic risk but 35% bleeding risk, more common in patients taking anticoagulation [16]. Our cohort was similar, with no thromboembolic events and increased rates of postpartum hemorrhage. A large multicenter study of women with Fontan circulation and pregnancy by Ladouceur et al. included 108 pregnancies in 84 women across 13 centers. In that study, 30% of patients had an adverse cardiac event, which was associated with maternal baseline oxygen saturation <92% [17]. Our study has lower rates of maternal adverse cardiac events, similar to a recent meta-analysis by Attachaipanich et al., which included 400 patients and 1260 pregnancies over a similar time period to our study; they noted a 6% risk of arrhythmia, 3% risk of heart failure, and no maternal mortality [2]. Importantly, none of these studies report any maternal deaths. Therefore, while the rates of adverse events are not minimal, most women with Fontan circulation who complete a successful pregnancy are likely not in the mWHO IV category.

In our study, we found a temporal increase in pregnancies over the 25-year study period (Figure *2*). While pregnancies were infrequent in the earlier years of the cohort, annual pregnancy volume increased during the contemporary era, with the highest number of pregnancies occurring in the most recent decade. This trend likely reflects the growing population of reproductive-aged women with Fontan circulation resulting from improved long-term survival and transition to adult congenital heart disease care. Although pregnancy frequency increased over time, a corresponding reduction in spontaneous abortion was not observed.

Pregnancy loss remained common throughout the study period, with spontaneous abortion occurring in more than half of all pregnancies. These findings suggest that while increasing numbers of women with Fontan circulation are pursuing pregnancy, the fundamental reproductive challenges associated with Fontan physiology persist.

While Ladouceur et al. included only pregnancies progressing beyond 20 weeks of gestation, others have evaluated risk factors for spontaneous abortion [17]. Wazni et al. [5] reported on outcomes of 20 patients from another program in the United States and found lower pre-pregnancy maternal SpO2 to be associated with spontaneous abortion. However, the average pre-pregnancy SpO2 differed by only 2% between the spontaneous abortion and live birth groups; oxygen saturation exceeded 90% in both groups, and they utilized a complex Bayesian model for analysis. We did not find a statistical association between hypoxia and spontaneous abortion in our cohort (Figure *1*), though we chose a simple and more clinically useful definition of hypoxia, which has been previously used [15]. Furthermore, Wanzi et al. found that uRV and moderate to severe atrioventricular (AV) valve regurgitation were also associated with spontaneous abortion [5], though they had more patients with uRV (n =10) than our cohort, and we did not have any patients with more than moderate AV valve regurgitation. Continued efforts to identify predictors of successful pregnancy and strategies to mitigate pregnancy loss in women with Fontan circulation remain necessary.

Our study also describes the use of maternal invasive hemodynamic monitoring during delivery, which has not been robustly reported. At our institution, the use of invasive monitoring is discussed in our multidisciplinary cardio-obstetric conferences before delivery on a case-to-case basis and is influenced by the cardiac and obstetric anesthesia teams, whose preferences have evolved over time. In our cohort, eight (38%) deliveries utilized either a central venous catheter or arterial line. While some suggest that invasive monitoring is rarely required for delivery in patients with complex congenital heart disease [18], there are instances where this can be helpful, and it is often recommended in the anesthesia literature [19]. The primary reason for the use of invasive monitoring was for cesarean delivery, with five of the 11 cesarean deliveries performed with an arterial line or central venous line. Central venous pressure monitoring can be helpful given preload-dependent circulation, though it is often not required. In the three patients for whom an arterial line was used for vaginal delivery, one was due to the patient's mild ventricular dysfunction, one was due to the complexity of congenital heart disease, and one was used in a patient admitted at a community hospital who delivered in the intensive care unit with limited institutional experience in Fontan pregnancy. Invasive monitoring for the peripartum period in patients with Fontan should be individualized based on the patient's hemodynamic status and ventricular function; our institution's most recent practice is typically the use of an arterial line during cesarean delivery.

This study has several important limitations that should be considered when interpreting the findings. As a single-center retrospective analysis, the results may not be generalizable to broader populations of women with Fontan circulation, particularly those managed in non-tertiary or resource-limited settings. The sample size was relatively small (though similar to prior single-center reports) [2-7,9], limiting statistical power to detect associations between clinical characteristics and outcomes. Early pregnancy losses may not have been systematically captured within the medical record, potentially resulting in underrepresentation. Additionally, documentation biases inherent to retrospective clinical data may have influenced case identification and outcome ascertainment. Missing or incomplete documentation, particularly regarding detailed fetal data, may have led to underestimation or misclassification of certain outcomes. Additionally, management strategies have evolved over the 25-year study period, introducing heterogeneity in clinical practice that could influence maternal and fetal outcomes. Similarly, interpretation of temporal trends in pregnancy should be made with caution. The observed increase in annual pregnancy volume may reflect improved survival among women with Fontan circulation but may also have been influenced by evolving referral patterns, increasing experience with cardio-obstetric care, and improved capture of pregnancies within the medical record over time. Information on socioeconomic factors (level of education, employment status, income) was not available, though these are known to impact pregnancy outcomes. The retrospective observational design precludes assessment of causality, and unmeasured confounders, medication adherence, or subtle variations in cardiac function, which may have influenced results. An additional limitation is that the multivariable regression model may have been overfitted because a large number of covariates were analyzed relative to the small number of events, reducing statistical power and limiting confidence in negative findings from the adjusted analyses. Despite these limitations, the study provides valuable insight into pregnancy outcomes in this high-risk population.

Conclusions

In this 25-year experience of pregnancy in women with Fontan circulation, we report no maternal mortality or neonatal deaths, and 10% adverse cardiac events. However, spontaneous abortion, preterm birth, and low birthweight were common. Although the number of pregnancies increased over the study period, pregnancy loss remained frequent and exceeded live births overall. The absence of term pregnancies among patients with hypoxia underscores the need for careful preconception counseling and multidisciplinary management of patients with Fontan circulation, especially those with baseline SpO2 <90%.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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Disclosures

Human subjects: Informed consent for treatment and open access publication was obtained or waived by all participants in this study. Biomedical Sciences Institutional Review Board, The Ohio State University issued approval 2023H0313. **Animal subjects:** All authors have confirmed that this study did not involve animal subjects or tissue. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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