Circulation: Cardiovascular Quality and Outcomes

ORIGINAL ARTICLE

Pregnancy in Women With a Fontan Circulation

A Systematic Review of the Literature

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BACKGROUND: The Fontan operation has provided life-saving palliation and adult survival for individuals born with single ventricle physiology. Many now seek advice about safe pregnancy. Little data are, however, available, consisting mainly of anecdotal experience and small series. This article seeks to review the published literature and identify lessons learnt from this collective experience.

METHODS AND RESULTS: We conducted a systematic review to evaluate maternal and fetal outcomes of pregnancy in women with a Fontan circulation. Among 1150 studies that were screened, 6 studies had sufficient longitudinal data points to qualify for meaningful inclusion, yielding 255 pregnancies in 133 women after Fontan procedure resulting in 115 live births (45%; including reports from 1986 to 2015). There was a total of 137 pregnancy losses (69%), with 115 miscarriages (45%), 19 elective terminations of pregnancy (7%), 2 stillbirths (1%), and 1 ectopic pregnancy (1%).The most common cardiovascular adverse events were supraventricular arrhythmia affecting 8.4% (range, 3%–37%) and heart failure affecting 3.9% (range, 3%–11%) of pregnancies. These complications were successfully managed with conventional approaches. No maternal deaths were reported. Postpartum hemorrhage was the predominant obstetric complication affecting 14% of the patients. Most patients were on antiplatelet agents (27%) or anticoagulants (50%) whereas only a minority (11%) were on neither. Among the 115 live births, 68 were premature (59%), 17 were small for gestational age (20%), and neonatal death occurred in 6 patients (5%).

CONCLUSIONS: The most commonly reported cardiovascular complications in patients with Fontan physiology–associated pregnancy were arrhythmia and heart failure. Miscarriages were highly prevalent as was prematurity and intrauterine growth restriction. Postpartum hemorrhage seems to be the most common obstetric complication. Large-scale data sets are needed to confirm these early observations and address the late sequelae of pregnancy in women with a Fontan circulation.

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WHAT IS KNOWN

- Fontan palliation is a life-saving surgical procedure for patients with complex congenital heart disease.
- Fontan palliation results in derangement of the normal cardiovascular hemodynamics that might adversely affect pregnancy.

WHAT THE STUDY ADDS

- Arrhythmias and heart failure are the most frequent cardiac complications among women after Fontan palliation during pregnancy.
- Miscarriages are common in these patients, and successful pregnancies can be frequently complicated with premature deliveries and intrauterine growth retardation.
- Postpartum hemorrhage is common among these patients.

Unpalliated individuals born with single ventricular (SV) physiology used to have high mortality during the childhood years. The Fontan operation surgically redirects caval venous return directly to the pulmonary circulation without first passing through the single ventricle heart chamber. These abnormal connections, though remedial of cyanosis, ventricular volume load, and unbalanced pulmonary blood flow, create exceptional challenges for the cardiovascular system.[1,2] The hallmark cardiovascular features of the Fontan operation are summarized in Table 1.[3–7]

Despite these profound cardiovascular challenges, survival into adulthood is now commonplace.[8] Many women with such palliated SV physiology now strive to achieve safe pregnancies. However, because late cardiovascular morbidity and extracardiac organ dysfunction occur with increasing frequency, it is imperative to carefully consider potential adverse interactions between the cardiovascular system and pregnancy.[9–11] The adverse cardiovascular physiology and late morbidity of Fontan circulations may potentially aggravate or indeed itself be aggravated by the physiology of pregnancy, including both the hemodynamic impact and the prothrombotic risks.

Given the potentially complex series of interactions and influence on pregnancy outcomes, this article aims to conduct a systematic review and summarize the published literature on pregnancy among women with a Fontan circulation and use this to outline the lessons learnt from this collective wisdom.

METHODS

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure. A systematic review of the literature that evaluated maternal and fetal outcomes during pregnancy in women with a Fontan circulation was conducted. All studies were considered eligible if they included ≥5 pregnancies and if pregnancy and cardiovascular outcomes information was included. Case reports or small case series (ie, ≤5 pregnancies), and studies reporting delivery only data, without maternal cardiac information, were excluded.

We searched PubMed and the Cochrane Library for all studies published in English between years 1990 and 2017 with search criteria including the following terms: Pregnancy and any of the following Fontan, single ventricle, double inlet left ventricle, tricuspid atresia, hypoplastic left heart syndrome, hypoplastic right heart syndrome, unbalanced atrioventricular septal defect, or univentricular atrioventricular connection.

RESULTS

A total of 1150 studies were reviewed for eligibility (Figure 1). Of these, the majority was excluded (939 studies) based on the exclusion criteria. The most common reason being that the articles dealt with fetal SV heart rather than maternal SV heart. Of these excluded studies, 29 reports were single cases or small case series of <5 pregnancies. These excluded reports included a total of 31 women, having 37 deliveries, among whom 2 had 4 consecutive pregnancies each, and 2 had twin pregnancies. There were no deaths reported in these case reports. Of the 13 potentially eligible studies, 7 were excluded based on different population selection (ie, not only women with a Fontan circulation), different outcomes not relevant to this report, and no data about pregnancy outcomes.[12–18] The final 6 studies included in this report included a total of 255 pregnancies among 133 women with a Fontan circulation and SV physiology.[19–24] Two independent researchers (A.G. and G.R.V.) assessed whether inclusion and exclusion were performed correctly. In case of disagreement, an agreement was negotiated. References of selected papers were crosschecked for other relevant stud-

Table 1. Key Cardiovascular Features of the Fontan Circulation

Obligatory central and systemic venous hypertension in the range of 10–20 mm Hg
Risk of arrhythmias
Nonpulsatile flow to the lungs
Hepatic congestion
Depressed resting and exercise cardiac output
Preload deprivation of the univentricular heart
Relatively fixed pulmonary vascular resistance such that with increased cardiac output pulmonary artery and venous pressures rise
Higher arterial impedance with poorer ventricular–vascular coupling
Thrombophilic tendency
Bleeding propensity

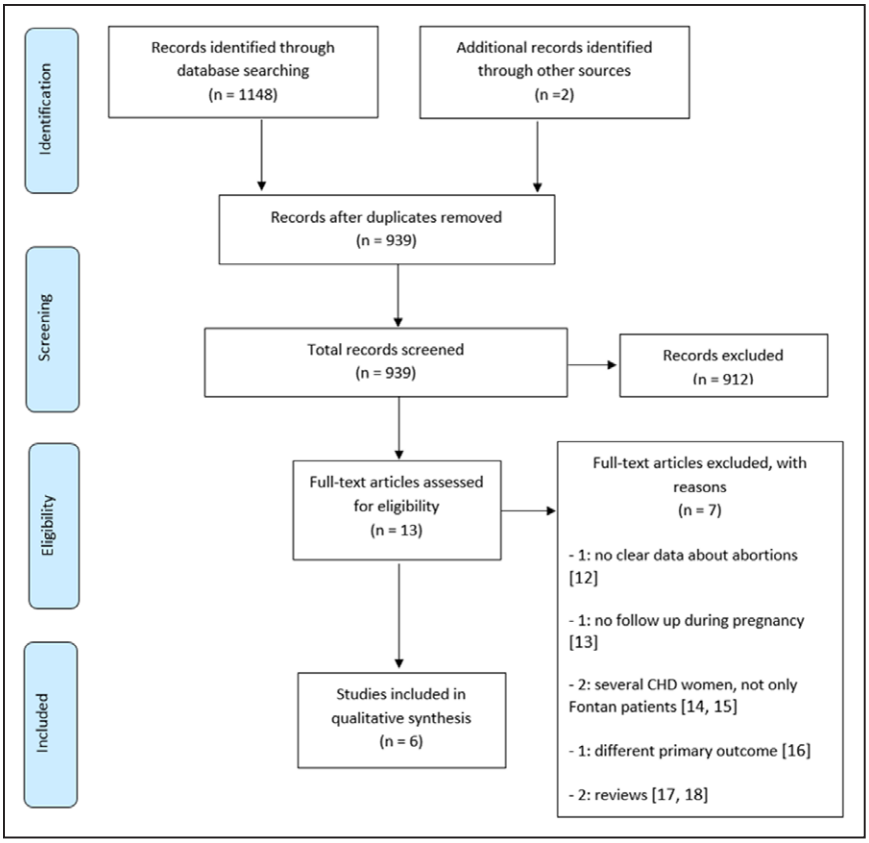

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram—study identification, selection, and exclusions. CHD indicates congenital heart disease.

ies. The studies by Pundi et al[22] and Canobbio et al[19] might have some overlap in the included patients. There was inadequate information to discern those patients who had overlapping information.

Patient Characteristics

Underlying anatomic description and the type of surgical correction were not uniformly reported. However, tricuspid atresia appeared to the most common underlying cause, and there was an equal distribution of atriopulmonary and total cavopulmonary Fontan (Table 2). There was limited prepregnancy information; however, arrhythmias appeared to be relatively common (Table 2).

Maternal Cardiovascular Complications

Mortality and Later Cardiovascular Morbidity

There were no reported maternal mortalities in the reported literature. However, there were at least 2 potentially life-threatening complications associated with pulmonary embolism in the immediate postpartum period.[14, 17] Late postpartum effects are poorly documented in the published literature. Pundi et al[22] reported 1 death, 11 years after successful pregnancy (cause of death unknown), and 1 cardiac transplantation, for progressive heart failure (HF), 1 year after therapeutic termination (Tables 2 and 3; Figure 2).

Supraventricular Arrhythmia

The most common cardiovascular complication during pregnancy was supraventricular arrhythmia, described in 15 of 198 pregnancies with available data (ie, overall prevalence of 8.4%; range, 3%–37%). Arrhythmia occurred mostly in the third trimester and responded to conventional treatment approaches described in Table 3.

Heart Failure

The second most common cardiovascular complication was HF, described in 7 of 198 pregnancies (overall prevalence, 3.9%; range, 3%–11%). HF was observed in the postpartum period in 4 of the 7 cases reported across the studies. In at least 1 case, HF was associated with persistent atrial fibrillation.

Other Cardiovascular Complications

Pundi et al[22] described bradycardia in 3 of 19 pregnancies, requiring pacemaker therapy during pregnancy. Two of these pregnancies resulted in premature delivery at 27 and 29 weeks, respectively.

Anticoagulation, Antiplatelet Therapy, and Hemostatic Complications

Only 4 studies reported data on anticoagulation or antiplatelet strategies during pregnancy and hemostatic complications. Most patients were on antiplatelet agents (27%) or anticoagulants (50%). In 12 of the

Table 2. Overview of the Literature on Pregnancy in Fontan Patients

Study	Study Period	Publication Year	Type of Study	No. of Subjects	No. of Pregnancies	Anatomic Diagnosis	Type of Fontan	Characteristics Before Pregnancy	Cardiovascular Complications (% of Total Pregnancies)	Pregnancy Loss (% of Total Pregnancies)
Canobbio et al[19]	…	1996	Retrospective (Mayo Clinic and UCLA medical center registries)	21	33	T.Atresia: 7 (50%) DORV:3 (21%) DILV: 2 (14%) HLHS: 1 (7%) Others: 2 (14%)	AP: 8 (57%) RA-AV: 3 (21%) TCPC: 3 (21%)	V. dysfunction: 1 (3%) AVVI: 1 (3%) Arrhythmia: 3 (21%)	HF: 1 (3%) SVT: 1 (3%)	Miscarriages:13 (39%) Elective TOP: 5 (15%)
Drenthen et al[20]	1986–2003	2006	Retrospective (Netherlands and Belgium CONCOR registry)	6	10	T.Atresia: 18 (47%) DORV: 3 (8%) DILV: 7 (18%) PA/IVS: 3 (8%) Others: 7 (18%)	AP: 22 (60%) RA-AV: 8 (21%) TCPC: 3 (8%)	Sev dysfunction: 5 (13%) AVVI (III/IV): 6 (16%) Arrhythmia: 19 (50%)	SVT: 1 (10%) NYHA ↓: 2 (20%)	Miscarriages: 5 (50%) Ectopic pregnancy: 1
Gouton et al[21]	2000–2014	2015	Retrospective (French M3C network)	37	59	T.Atresia: 19 (51%) DORV: 3 (8%) DILV: 7 (19%) Others: 8 (22%)	AP: 6 (16%) TCPC: 31 (84%)	Mild dysfunction: 4 (11%) AVVI (III/IV): 0 (0%) Arrhythmia: 7 (19%)	HF: 3 (5%) SVT: 3 (5.1%) SE: 2 (3.4%)	Miscarriages 16 (27%) Elective TOP: 4 (7%) Stillbirth: 1 (3%)
Pundi et al[22]	1973–2015	2016	Retrospective (Mayo Clinic medical record)	35	70	Dom RV: 3 (16%) Dom LV: 13 (68%) Common: 3 (16%)	AP: 9 (47%) TCPC: 7 (37%) Other: 3 (16%)	EF: 49%±5%	HF: 2* (10.5%) SVA: 7* (36.8%) PM: 3* (15.8%)	Miscarriages: 35 (50%) Elective TOP: 6 (9%)
Zentner et al[23]	…	2016	Retrospective (Australia and New Zealand Fontan Registry)	20	40				HF: 1† (7.1%) Arrhythmia (DCR): 1† (7.1%)	Miscarriages: 17 (43%) Elective TOP: 4 (10%) Stillbirth: 1 (3%) No information: 2 (5%)
Cauldwell et al[24]	1994–2014	2016	Retrospective (multicenter in England)	14	43	T.Atresia: 7 (50%) Dom RV: 4 (29%) Dom LV: 10 (71%)	TCPC: 9 (64%) AP: 5 (36%)	Arrhythmia: 9 (64%) Mild dysfunction: 1 (7%)	Desaturation: 1 SVT: 3	Miscarriages: 29 (67%)
Total				133	255		AP: 54 RA-AV: 11 TCPC: 53 Other: 3		SVT: 15 (8.4%) HF: 7 (3.9%)	Miscarriages: 115 (45%) Elective TOP: 19 (7%) Stillbirth: 2 (1%) Ectopic pregnancy: 1 (1%) Total Pregnancy Loss: 137 (54%) No information: 2 (1%)

Data are listed according to maternal cardiovascular complications during pregnancy and total pregnancy losses. French M3C network denotes 13 centers of the French M3C network for patients with complex cardiac malformations. CONCOR registry was funded by the Netherlands Heart Foundation and a Belgian tertiary medical center's adult congenital heart disease database. AP indicates atriopulmonary fontan; AVVI, *Atrio-ventricular valve insufficiency*; CONCOR, congenital corvitia; DCR, direct current cardioversion; DILV, double inlet left ventricle; Dom, dominant ventricle; DORV, double outlet right ventricle; EF, *ejection fraction*; HF, heart failure; HLHS, *hypoplastic left heart syndrome*; LV, *left ventricle*; NYHA, New York Heart Association; PA/IVS, pulmonary atresia intact ventricular septum; PM, pacemaker during pregnancy; RA-AV, right atrial atrioventricular Fontan; RV, *right ventricle*; SE, systemic embolism; SVA, supraventricular arrhythmia; SVT, supraventricular tachycardia; T.Atresia, tricuspid atresia; TCPC, total cavopulmonary connection; TOP, *termination of pregnancy*; UCLA, University of California Los Angeles; and V., ventricle.

*Among 19 available data pregnancies.

†Among 14 available data pregnancies resulted in a birth.

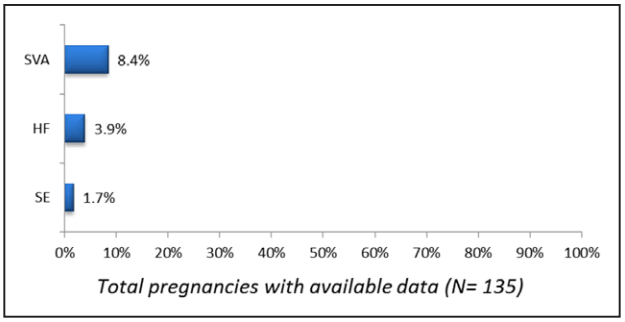

Figure 2. Cardiovascular complications.
HF indicates heart failure; SE, systemic embolism; and SVA, supraventricular arrhythmia.

total 113 women (11%) with available data, no anticoagulation or antiplatelet was used. Overall bleeding complications occurred in 28 pregnancies (25%), including 12 (11%) with antepartum hemorrhage and 16 patients with postpartum hemorrhage (PPH; 14%). PPH was not associated with a specific anticoagulation regimen. This complication occurred in patients with anticoagulants, as well as in patients with antiplatelet therapy or no treatment (Table 4).

Obstetric and Fetal Complications

Miscarriages and Prematurity

There were a total of 137 pregnancy losses among 255 pregnancies (54%; Tables 2, 4 through 6; Figure 3). Of these, 115 (45%; range, 27%–67%) were spontaneous miscarriages, 19 (7%) were medically or surgically induced termination of pregnancy, 1 was an ectopic pregnancy (1%), and there were 2 stillbirths (1%). In addition, there were 68 premature deliveries (59%) and 6 neonatal deaths (5%) among 115 live births (Table 5).

Causes of prematurity were not specified, particularly iatrogenic prematurity induced by an early planned delivery for maternal cardiac reasons was not mentioned. However, premature rupture of membranes was reported in 10 patients among a total of 161 pregnancies (6.2%), and antepartum hemorrhage including abruption placentae was diagnosed in 10 pregnancies among a total of 109 pregnancies (10.9%). In Gouton et al[21] study, atriopulmonary Fontan was diagnosed in 3 pregnancies. At the time of this bleeding events, the women were receiving antiplatelet therapy, prophylactic anticoagulation with unfractionated heparin, and therapeutic anticoagulation with low molecular weight heparin, respectively (Table 6).

Mode of Delivery

Overall, in the reported cohort, cesarean-section (CS) was performed in 40 of 70 reported pregnancies, that is, a prevalence of 57.1% (range, 42%–79%). Canobbio et al[19] reported 11 CS among 14 women with live births and with available data (78.6%). Indications for CS included 1 preterm labor, 1 failure to progress, 1 footling breech presentation, and 8 unknown. Drenthen et al[20] described CS in 3 of the 4 viable pregnan-

Table 3. Maternal Cardiovascular Complications and Management

Study	Maternal CV Complication	Gestational Age	Management	Outcome
Canobbio et al[19]	SVT: 1	27 and 38.5 GW	Digoxin+verapamil	Resolved
	HF: 1	1 wk post-delivery	Oxygen+afterload-reducing agents	Resolved
Drenthen et al[20]	SVT (AF): 1	33 GW	150 mg failed flecainide+ECV	Resolved
	Exercise intolerance: 2	Third trimester	None	Resolved after delivery
Gouton et al[21]	SVT: 1 persistent AF SVT: 1 paroxysmal AFL SVT: 1 paroxysmal AF SE: 1 TIA SE: 1 ICT HF: 1 HF: 3	First and second trimesters First trimester 18 GW 32 GW Post-partum	Chemical cardioversion with amiodarone Sotalol Propranolol Antiplatelet drugs 4000 anti-Xa UI/24 h Because of persistent AF (cardioversion with amiodarone) …	Resolved No reported adverse outcomes No reported adverse outcomes No reported adverse outcomes No reported adverse outcomes Resolved No reported adverse outcomes
Pundi et al[22]	SVT: 1 AFL	Second trimester	Atenolol+verapamil+nonspecified cardioversion+enoxaparin	Resolved after cardioversion
	SVT: 6	…	Calcium channel blockers or β-blockers	No reported adverse outcomes
	HF: 2	…	…	No reported adverse outcomes
Zentner et al[23]	SVT: 1	…	Electrical cardioversion	No reported adverse outcomes
	HF: 1	Postpartum	Diuretics	No reported adverse outcomes
Cauldwell et al[24]	SVT: 3	Peri-delivery	2 spontaneous terminations and 1 cardioversion with amiodarone	No reported adverse outcomes

… denotes unknown or not reported. AF indicates atrial fibrillation; AFL, atrial flutter; CV, cardiovascular; ECV, electrical cardioversion; GW, gestational week; HF, heart failure; ICT, intracardiac thrombus; SE, systemic embolism; SVT, supraventricular tachycardia; and TIA, transient ischemic attack.

Table 4. Anticoagulation, Antiplatelet Management, and Hemostatic Outcomes

Study	Women/Total Pregnancies	Viable Pregnancies	Anticoagulation Regimens				Hemorrhagic Events		Thromboembolic Events
			Antiplatelet	Therapeutic AC	Prophylactic AC	None	APH	PPH	
Gouton et al[21]	37/59 (37 women with available data)	37 (1 twin pregnancy)	12 (22.2%)	27 (50%)	12 (22.2%)	4 (7.4%)	3	3	3 (1 submassive PE)
Pundi et al[22]	35/70 (19 women with available data)	29	12 (63.2%)	3 (15.8%)	2 (10.5%), only immediately pre-delivery	5 (26.3%)	2	1	0
Zentner et al[23]	27/40 (14 women with available data)	14	6 (43%)	5 (35.7%)*	NR*	3 (21%)	4 (2 subchorionic APH)	6 (3 needed transfusion)	0
Cauldwell et al[24]	14/43 (8 women with available data)	14	0 (0%)	0 (0%)	8 (100%)	0 (0%)	3	6 (1 requiring ICU)	1 (submassive PE)
Total	113/212	94	30 (27%)	35 (31%)	22 (19%)	12 (11%)	12 (11%)	16 (14%)	4 (4%)

AC indicates anticoagulation; APH, antepartum hemorrhage; ICU, intensive care unit; NR, not reported; PE, pulmonary embolus; and PPH, postpartum hemorrhage.

*Not reported as therapeutic or prophylactic.

cies (75%). The authors reported indications for CS as follows: 1 preterm labor, 1 breech presentation, and 1 elective CS with unreported indication. Gouton et al[21] described 16 CS in 38 completed pregnancies (42.1%; including a twin pregnancy). Pundi et al[22] reported CS in 10 of 14 (71.4%) women where this information was available. Cauldwell et al[24] reported CS in 7 of 14 Fontan pregnancies. Additional obstetric and noncardiac complications are listed in Table 6.

DISCUSSION

Understanding the interactions between pregnancy and Fontan hemodynamics, as well as being aware of the potential obstetric complications that may arise, is fundamental to providing counseling and sound medical care for women with a Fontan circulation undergoing pregnancy. In this review, we demonstrated that although no deaths were demonstrated, there are many potential serious complications that arise during pregnancy associated with a Fontan circulation. Probably, these early series included typically those patients after the Fontan procedure with good ventricular function, no severe valve dysfunction, and good exercise capacity. A selection bias in the available literature seems likely as women with ventricular dysfunction, or other problems will have been counseled against pregnancy. The main cardiovascular complications were arrhythmia and heart failure, and the dominant obstetric complications were miscarriages, PPH, prematurity, and most likely also intrauterine growth restriction although the numbers were too small to be certain. The absence of a strong association between maternal anticoagulation and bleeding might suggest that factors other than maternal anticoagulation could contribute to PPH in this patient population.

Cardiovascular Complications

Supraventricular arrhythmia was the most common cardiovascular adverse event observed in the published series, occurring in a tenth of women. In all, the arrhythmia was responsive to treatment approaches, including β-blocker therapy, calcium channel blockade, sotalol, and amiodarone. For acute termination, flecainide (category C) and amiodarone (category D), as well as electrical cardioversion, were applied successfully. Most of the supraventricular arrhythmia episodes occurred after the first trimester. Pregnancy is well recognized to lower the threshold for ventricular and atrial arrhythmia through a variety of neurohormonal mechanisms.[21] Fontan patients also have an inherent propensity toward atrial arrhythmia. This is driven by sinus node disease, surgical scar burden, altered atrial tissue organization, and acquired atrial and ventricular myocardial connexon injury. This synergistic environment between pregnancy and Fontan circulations provides an ample milieu for arrhythmia generation.

The second most frequent cardiovascular complication was acute HF. Interestingly, HF occurred not only in the third trimester but also frequently in the postpartum period. There may be multiple reasons or a combination of reason for this: (1) Fluid shifts occurring in the early postpartum period as the uterus contracts and auto-boluses ≈250 cc of blood in an already volume loaded circulation. Furthermore, there may be persistent fluid overload for weeks after post-partum which might impact development of acute HF. (2) Diastolic dysfunction in Fontan patients is often under-recognized and occurs frequently in asymptomatic patients.[25,26] (3) At term, diminution in myocardial strain has also been demonstrated in the peripartum period.[27]

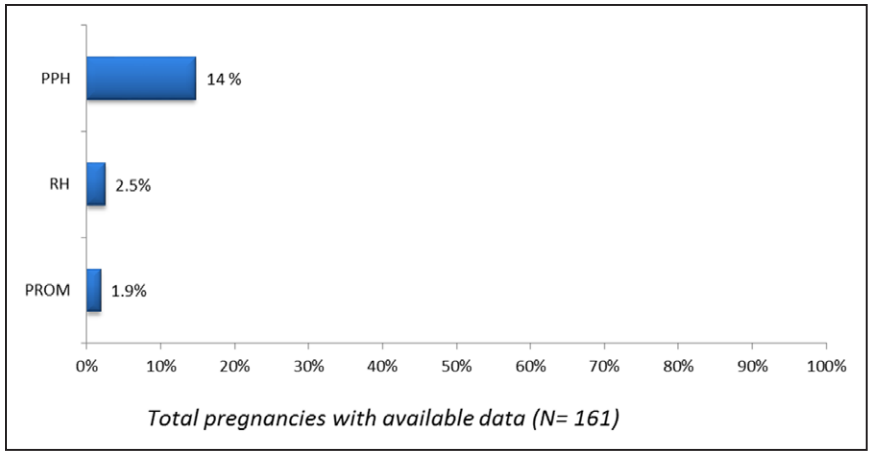

Figure 3. Obstetric complications. PPH indicates postpartum hemorrhage; PROM, premature rupture of membranes; and RH, retroplacental hematoma.

The management of acute HF is similar to nonpregnant Fontan patients, with the exception of avoiding fetotoxic medications (ie, angiotensin-converting enzyme inhibitors and angiotensin receptor blockade, no data as yet on neprolysin inhibition –based on Food and Drug Administration categories).[28] Diuretics should be used with caution in Fontan patients to avoid too low preload. It is important to evaluate for occult arrhythmia, pathway thrombosis, gestational hypertension and preeclampsia, and anemia as potential causes for HF. These potential triggers may occur on the back of unrecognized underlying pathway obstruction, elevated pulmonary vascular resistance, and systolic or diastolic disease of the systemic ventricle and need prompt treatment. Defining HF is always difficult in the Fontan population because factors other than primary ventricular dysfunction, such as elevated pulmonary vascular resistance, could potentially result in symptoms. Hence, it is important to have a broad perspective in the evaluation of these patients and not be limited to treating primary ventricular dysfunction. In addition, pregnancy itself may mimic severe heart failure symptoms, such as shortness of breath and edema.[29] Finally, the possible adverse impact of pregnancy on long-term outcome in Fontan patient remains unclear because of the lack of sufficient data. Irreversible deterioration may occur because of the increased cardiac output, occurrence of arrhythmia, or possible pulmonary embolisms leading to elevated pulmonary pressures. The delicate balance in the Fontan physiology may be disturbed by the pregnancy and not restored afterward.

Obstetric Complications

The CS rate was high in the reported literature, documented in ≈2/3 of women. This is much higher compared with the national average of the countries involved in the study which ranges from 11% to 32% during the study time period.[30] Indications for CS included preterm labor, failure to progress, and breech presentation. Vaginal delivery remains the more preferable approach to delivery because it is associated with a lower risk of PPH and a better fetal outcome.[12,31] However, this is in the context of a high-risk mother, who might need urgent CS because of factors, such as maternal hemodynamic decompensation.

The most frequent obstetric complications detected was PPH, occurring in half of women in the larger series. In the general population of pregnant women, PPH occurs at a rate of 2.9% to 6%, and the rate of hemorrhagic complications while on anticoagulation in the postpartum period is estimated between

Table 5. Neonatal Complications

Study	Live Births/Total Birth	PD	SGA	CHD	ND
Canobbio et al[19]	15/33 (45%)	1	NR	1	0
Drenthen et al[20]	4/10 (40%)	2	2	0	1
Gouton et al[21]	38/59 (64%)	25	4	2	1
Pundi et al[22]	29/70 (41%)	18*	3*	2*	1
Zentner et al[23]	15/40 (40%)	12	NR	NR	2
Cauldwell et al[24]	14/43 (33%)	10	8	0	1
Outcomes	115/255 (45%)	68 (59%)	17 (20%)†	5 (5%)†	6 (5%)

CHD indicates congenital heart disease; ND, neonatal death; NR, not reported; PD, premature delivery; and SGA, small for gestational age.

*Twenty-nine live births were reported, but only 22 had information on outcomes.

†Overall percentage was calculated after exclusion of the cohorts which did not report the particular variable.

Table 6. Maternal Noncardiac Complications During Pregnancy and Frequency of Premature Rupture of Membranes

Study	Noncardiac Complications (Timing in the Pregnancy; %)	Premature Rupture of Membranes (%)
Canobbio et al[19]	PHE: 2 (NR; 6%); PL: 1 (at 28 wk; 3%)	PROM: 1 (at 34 wk; 3%)
Drenthen et al[20]	HTN: 1 (NR; 10%)	PROM: 1 (at 25 wk; 10%)
Gouton et al[21]	RF: 1 (second trimester; 2%); Anemia with transfusion: 1 (third trimester; 2%); PE: 1 (post-partum; 2%)	PROM: 7 (12%)
Pundi et al[22]	HTN: 1 (third trimester; 5%); Preeclampsia: 1 (NR; 5%)	…
Cauldwell et al[24]	PE: 1 (peripartum; 2%)	PROM: in 2/14 women (14%)

HTN, hypertension; NR, not reported; PE, pulmonary embolism; PHE, peripheral edema; PL, preterm labor; PROM, premature rupture of membranes; and RF, renal failure.

2% and 11%.[32] Uterine atony is probably the most predominant cause of PPH. This may well be driven by the general practice of restricting uterotonic usage because of concerns for tachycardia, hypotension, and fluid retention in women with cardiac disease. Its safe use, however, has been demonstrated in a recent publication.[33] It is also plausible that abnormal vascular malformations, underlying liver disease, and thrombotic disorders in the Fontan population could have contributed to PPH.[34]

In this review, a likely contributing factor to PPH was antiplatelet and anticoagulant therapy; however, this association is not straightforward. In Cauldwell's series, where women were managed only on prophylactic low molecular weight heparin and was stopped well before delivery, the incidence of bleeding was still high.[24] It is worthy to note that bleeding risk in Fontan patients outside of pregnancy is a recognized and perhaps under-reported phenomenon.[35]

Antepartum pulmonary embolism, and cerebral ischemic events, was denoted in isolated cases only. The Fontan state itself, even in the most current iterations of the circulation, as well as pregnancy per se, represents a prothrombotic state.[34] Procoagulants increase (factors 5, 8, Von Willebrand factor, and fibrinogen) and greater resistance to endogenous anticoagulants (decreased protein C, S, and more placental tissue plasminogen activator) occurs during pregnancy.[29] It is, therefore, not unreasonable to consider prophylactic therapeutic anticoagulation during pregnancy after individualized assessment of risks and benefits. This poses a therapeutic conundrum, balancing risks of bleeding versus thrombosis. We recommend therapeutic anticoagulation for pregnant patients with Fontan circulation who have prepregnancy history of arrhythmias or develop arrhythmias during pregnancy and for those with history of thromboembolic events.[21]

Fetal and Neonatal Complications

We found a high incidence of fetal and neonatal events. Miscarriages, isolated and recurrent, affected at least half of women. This high percentage needs special attention during counseling of women with Fontan procedure. Among live births, >50% were premature whereas SGA was diagnosed in 20%. It is likely that these early pregnancy losses, as well as the high incidence of prematurity and intrauterine growth restriction, are driven by a combination of factors, including placental insufficiency, intrinsic morphological uterine abnormalities, adverse hemodynamics including limited cardiac output, neurohormonal environment of the Fontan circulation, maternal medication (eg, β-blockers and vitamin K antagonists), and iatrogenic errors in decision making regarding time of delivery.[14,15,36–38] Overall, these phenomena lead to an adverse uterine environment for the developing fetus leading to neonatal sequela in case of live birth.[39,40]

Limitations

This review is limited by the small numbers included and by the incomplete nature of the individual data points within each study. The limited numbers could at least partly be attributed to subfertility or infertility and menstrual disorders that are commonly encountered in this population in addition to the counseling offered to the patients against the pregnancy. In addition, the outcomes (main and subgroup analysis) reported in each series, varies considerably leading to heterogeneity in the review. Furthermore, the limited number of patients with a systemic left ventricle, such as hypoplastic left heart syndrome, makes it difficult to comment on the role of the ventricular morphology in pregnancy outcomes among patients with Fontan physiology. There are several potential biases in the included studies. First, there may be an inherent reporting bias against mortality and severe morbidity outcomes. Second, there is likely a selection bias toward those patients with good Fontan hemodynamics whereas those patients with an unfavorable physiology strongly were advised against pregnancy. However, the impact of physician advice on pregnancy outcomes is still not yet clear and requires further studies. Finally, in several studies, data collection was a combination of patient response questionnaires or medical records review. This may preclude inclusion of women who experienced debilitating morbidity or were deceased. However, it may also have increased the accuracy of the reporting of termination and mis-

carriage, with information sharing supported by the anonymized data collection process. The potential for selection bias against sicker women is present in all studies, with these women potentially not surviving to consideration of or reaching child bearing age. In 2 papers, it is possible that data collection may have produced some overlap of women included.[19,22]

Conclusions

Retrospective review of the published literature in pregnant women with a relatively well-functioning Fontan circulation suggests that although pregnancy is relatively well tolerated, it remains a high risk undertaking, and the potential morbidities are both high and may be life threatening. Reporting and selection bias may have resulted in the apparent absence of actual mortalities. The most frequent cardiovascular adverse events were supraventricular arrhythmia and decompensated HF, all of which were treated with conventional treatment strategies. PPH, prematurity, and perhaps intrauterine growth restriction occur commonly. Antenatal counseling because of the high risk of recurrent miscarriages is of paramount importance. Clinicians should be aware of the hemorrhagic tendency during pregnancy in addition to the thrombotic tendency of the Fontan physiology and be ready to handle these complications in the peripartum period. The indications for anticoagulation and antiplatelet therapy among pregnant women with Fontan circulation need further investigation. HF can complicate the puerperium, and clinicians should be ready to tackle these complications. Further study of the potential causes of PPH, recurrent miscarriage, and prematurity, such as uterine atony and placental insufficiency, are needed. In addition, attention for the longer-term postpartum effects of pregnancy on the Fontan circulation is warranted.

ARTICLE INFORMATION

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Disclosures

None.

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