

REVIEW

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Pregnancy in the FONTAN palliation: physiology, management and new insights from bioengineering

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Abstract

Fontan palliation for the single ventricle results in a challenging and delicate physiological state. At rest, the body adapts to a low cardiac output and high systemic venous pressure. However, when physiological demands increase, such as in the case of exercise or pregnancy, this delicate physiology struggles to adapt due to the inability of the heart to pump blood into the lungs and the consequent lack of augmentation of the cardiac output.

Due to the advances in paediatric cardiology, surgery and intensive care, today most patients born with congenital heart disease reach adulthood. Consequently, many women with a Fontan circulation are becoming pregnant and so far data suggest that, although maternal risk is not high, the outcomes are poor for the foetus. Little is known about the reasons for this disparity and how the Fontan circulation adapts to the physiological demands of pregnancy.

Here we review current knowledge about pregnancy in Fontan patients and explore the potential role of computational modelling as a means of better understanding this complex physiology in order to potentially improve outcomes, particularly for the foetus.

Keywords: Fontan palliation, Congenital heart disease, Pregnancy, Foetus, Single ventricle

Key principles of pregnancy physiology

Normal pregnancy is associated with considerable physiological stress. As a dynamic process associated with significant haemodynamic and hormonal changes, it has a huge impact on the cardiovascular system. These changes are adaptive mechanisms to meet the increased metabolic demands of the foetus to ensure adequate uteroplacental circulation for foetal growth and development [1, 2]. Higher levels of oestrogen and progesterone cause increased vasodilation and reduced systemic vascular resistance. A healthy heart then increases heart rate and stroke volume

to increase cardiac output to the fetoplacental unit [3]. Cardiac output and stroke volume double, myocardial oxygen consumption increases by 20% and heart rate by 15–20% [2, 3]. In a normal pregnancy, there is also substantial activation of the renin-angiotensin-aldosterone system, which increases incrementally alongside oestrogen production. Cardiac structural changes occur as a consequence of these hemodynamic changes. The size and volumes of both ventricles increase as well as the thickness of the myocardium, accompanied by a transitory detriment in contractility. All of these changes (Fig. 1) are reversible following a normal pregnancy and are considered part of the body's adaptation to pregnancy [1–3].

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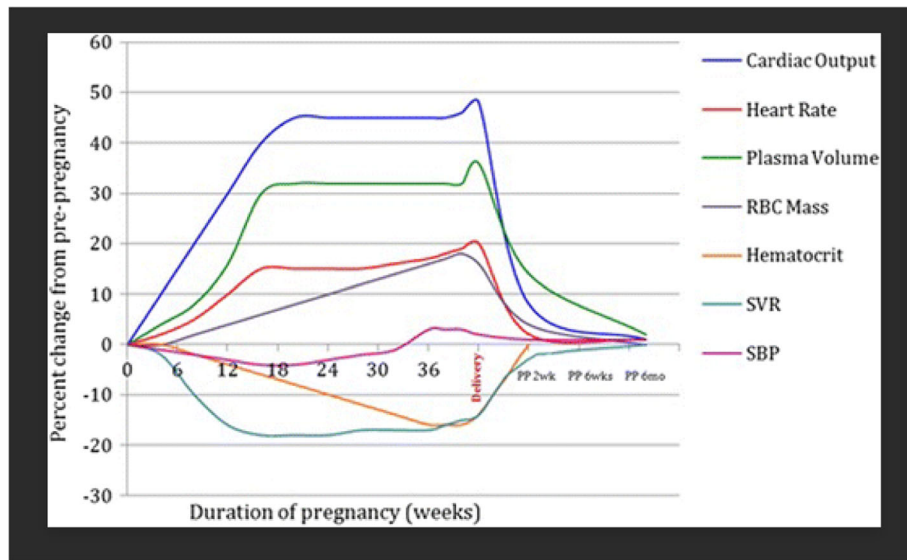


Fig. 1 Hemodynamic changes during pregnancy, delivery and the post-partum period. Reproduced with permission from Dr. DeFaria Yeh, Doreen [4]

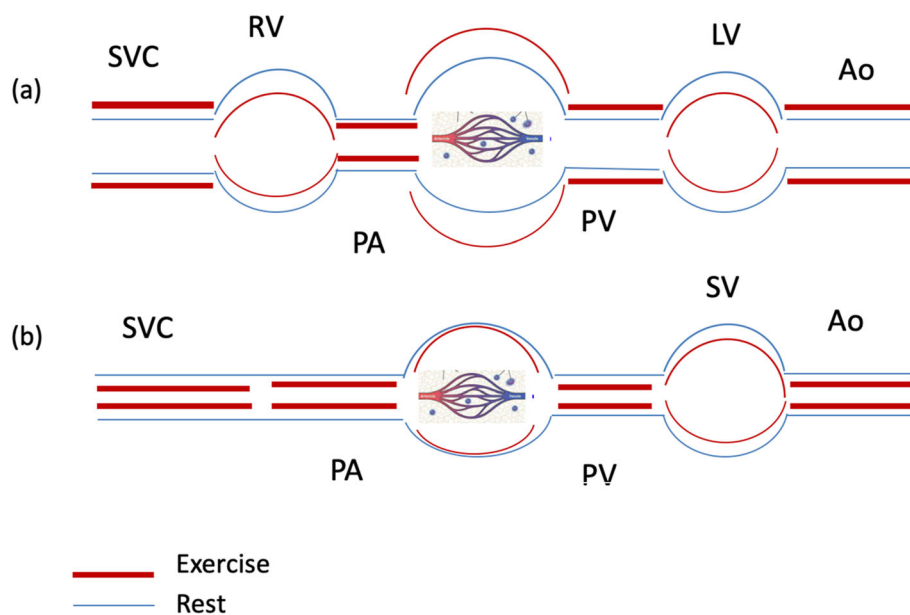


Fig. 2 Theoretical schematic illustration of circulatory pressure changes. **a** In a normal biventricular circulation, pressure is generated in the systemic ventricle (LV) to propel flow in the aorta and systemic circulation. The pre-pulmonary pump (RV) provides the pressure to propel flow in the pulmonary artery (PA) which then is distributed in the pulmonary circulation, but this is sufficient to maintain preload in the left atrium (LA). During exercise, the systemic vascular resistance falls such that there is little increase in mean LV pressure requirements. Therefore, a more substantial increase in the RV is required to pump blood anterogradely. **b** In a Fontan patient, the pulmonary flow is passive due to the lack of a sub-pulmonary ventricle and the flow through the pulmonary circulation depends on the pressure difference between the right atrium (RA) and LA. During exercise, transpulmonary flow can only be augmented by a reduction in pulmonary vascular resistance. (SVC: systemic venous flow, RV: right ventricle, PA: pulmonary artery, PV: pulmonary veins, LV: left ventricle, SV: single ventricle, Ao: aorta)

Key principles of the FONTAN physiology

A univentricular circulation describes a congenital heart defect where a biventricular repair is not possible [5]. The Fontan repair offers offloading of the single ventricle and improvement in oxygenation at the expense of low cardiac output and increased systemic venous pressure. In a Fontan circulation there is no pump to propel the blood into the pulmonary arteries since the systemic veins are directly connected to the pulmonary arteries [5]. The postcapillary energy is used to drive blood through the lungs, though hampered by the pulmonary impedance. Therefore, pulmonary vascular resistance (PVR) is the key factor influencing normal ventricular filling and in turn cardiac output (CO), rather than the contractility of the ventricle itself, as expected in a biventricular physiology [5].

Under exercise conditions, an increase in stroke volume and pulmonary artery pressure is observed in a biventricular circulation. A pre-pulmonary pump is required to generate the pressure and flow, which enables adequate left ventricular (LV) filling during exercise. However, in the absence of a pre-pulmonary pump and without adequate preload, CO cannot increase during exercise [6]. Furthermore, chronotropic incompetence may occur due to scar-related sinus node dysfunction and due to abnormal reflex control of heart rate or adrenergic dysfunction [7]. The lack of increase in CO can be partially explained by a number of factors, such as: chronotropic incompetence, impaired pulmonary function (as a consequence of thoracotomy), high pulmonary vascular resistance and inadequate augmentation of preload during exercise (Fig. 2). Therefore, patients with a Fontan circulation poorly tolerate preload changes due to their inability to increase CO against higher demands. Based on the same principle, pregnancy-related haemodynamic changes represent a considerable, additional burden for a univentricular heart [8].

The combination of two complex physiologies: pregnancy in FONTAN patients

Pregnancy is a challenge for the normal heart, based on the hemodynamic and structural changes described above, but a bigger challenge for the Fontan circulation. Understanding the interactions between pregnancy and Fontan hemodynamics, as well as being aware of the potential obstetric complications that may arise, is fundamental to provide counselling and sound medical care to women with a Fontan circulation undergoing pregnancy.

From a physiological standpoint, it must be borne in mind that the haemodynamic changes in pregnancy are not insignificant for Fontan patients. The low cardiac output resulting from single ventricle palliation is relatively well tolerated at rest but poorly when the demand increases in pregnancy. Increasing the CO by 50% is

simply not possible for the Fontan circulation. Furthermore, diastolic function is inherently abnormal in the Fontan [2, 3, 5, 6] and therefore the increase in heart rate that is associated with pregnancy further compromises the efficiency of the circulation.

The Fontan circulation is unique in that, in the absence of a sub-pulmonary ventricle, it relies on chronically elevated venous pressure in order to drive blood through the pulmonary vessels [9]. Elevated intrahepatic pressure is a long-term complication, which can lead to cirrhosis and portal hypertension. The additional effect of the foetus resting on the IVC and the increasing plasma volume results in further increasing portal venous pressure and this 'venous stagnation' may add to the adverse uterine environment for the foetus. This has not been studied but a similar situation exists in cirrhosis due to other causes. Pregnancy in women with cirrhosis is uncommon as fertility is reduced but the existing evidence points to poor foetal outcomes with increased rate of miscarriage, preterm labour and perinatal death [10].

Outcomes during pregnancy in a UNIVENTRICULAR physiology

Thanks to some landmark papers in the field of obstetric cardiology [5, 11, 12], we know that cardiac risk in pregnancy is increased by a number of key factors, namely reduced ventricular function, increased New York Heart Association (NYHA) functional class, cyanosis, the presence of a mechanical valve, reduced right ventricular function in the context of severe pulmonary regurgitation, significant left sided valve obstruction and risk of aortic dissection in women with connective tissue disorders. Several scores exist in order to translate these factors into a prediction of risk of adverse events in pregnancy for an individual woman. Similarly we know that foetal outcomes are also adversely affected by reduced ventricular function, increased NYHA functional class and cyanosis, but also by smoking and drugs such as warfarin.

However, the prevalence of univentricular hearts in the population is low and therefore Fontan pregnancies were not well represented in these studies. More recent data has suggested that, though traditional risk scores can help to predict events in the mother, foetal outcomes are significantly worse than expected [13].

The recent European Society of Cardiology (ESC) guidelines on heart disease in pregnancy put the 'good Fontan' in modified World Health Organisation (mWHO) III for risk, equating to a "significantly increased risk of maternal mortality or severe morbidity". For a Fontan "with any complication" the risk is mWHO IV: an extremely high risk of maternal mortality or severe morbidity. This advice comes from the little but increasing body of evidence available on this specific group of patients [14].

Theoretically we might expect therefore that the increased volume load of pregnancy will increase the risk of heart failure in the Fontan and that the enhanced adrenergic receptor excitability mediated by oestrogens and progesterone may trigger the development of arrhythmias. We might also expect that anticoagulation may cause problems for mother and foetus. It is logical that the foetus will be adversely affected by the reduced cardiac output and therefore foetal loss will be increased. All of these assumptions are borne out by the existing literature but it is perhaps surprising just how poor foetal outcomes are, even in a 'good' Fontan. Maternal outcomes are actually quite good. The ESC guidelines are correct in indicating the high risk to the foetus but the proposed high risk of maternal mortality or severe morbidity is not borne out by the literature.

Maternal complications

The existing literature suggests that indeed the most common risks to the mother in the Fontan pregnancy are of arrhythmias, heart failure and thromboembolic or bleeding events [15–17]. Overall, however, these risks are relatively low and patients have been reported as having been managed effectively and without long-term sequelae [18, 19]. Maternal death has not been reported (Table 1).

Arrhythmia

The most common maternal cardiac complication reported during pregnancy is supraventricular arrhythmia,

Table 1 Maternal, Obstetric and Foetal complications Reported in Fontan Pregnancies

Maternal complications	Overall prevalence (%)	Range (%)
Arrhythmias		
SVT	8.4%	3–37%
Heart failure	3.9%	3–11%
Thromboembolism		
Obstetric complications		
Ante-partum	11%	23%
Post-partum	43%	
Major haemorrhage	14%	
Foetal complications		
Miscarriages		27–69%
Prematurity		70–80%
SGA	60%	
IUGR	70%	
NND	5%	
PROM		10–20%

SVT Supraventricular tachycardia, SGA Small for gestational age, > haemorrhage (> 2 l), IUGR Intra uterine growth restriction, NND Neonatal death, PROM Premature rupture of membranes. See text for details

described in 15 out of 198 pregnancies with available data (overall prevalence of 8.4%; range 3–37%) [15]. Arrhythmia occurred mostly in the third trimester and responded to conventional treatment approaches, often cardioversion. In the largest single cohort in the literature, reporting data from the UK, 19 of the women included had a history of arrhythmia but only six of them were affected during pregnancy [18]. No ventricular arrhythmias have been reported but a few cases of bradyarrhythmia requiring pacing have been described [19].

Heart failure

Heart failure occurs in a significant minority of pregnancies in women with a Fontan circulation. A meta-analysis of the literature reported an overall prevalence of 3.9% (range 3–11%) with one case associated with persistent atrial fibrillation [15]. Women were largely asymptomatic prior to pregnancy [15].

Heart failure occurred, not only in the third trimester, but in the postpartum period in four of the seven cases reported [15]. This is not unexpected, as the haemodynamic changes in the post-partum period are profound. The uterus contracts and auto-transfuses 250 ml of blood into an already volume loaded circulation at a time when myocardial strain is reduced. Also the mass of the foetus is removed from the inferior vena cava, further increasing venous return. Diastolic dysfunction in Fontan patients may also contribute to their increased risk of heart failure in this scenario, as the Fontan heart struggles with the increased volume load.

It is likely that women with a Fontan circulation becoming pregnant have good function of the Fontan circuit and good contractility of the ventricle, which perhaps explains why prompt recovery of function after treatment is common and intractable ventricular failure is not described.

Thromboembolism

Pregnancy is a pro-thrombotic state. It has been known for many years that the Fontan operation and all its modifications also increases the risk of thromboembolism [15–17]. The reasons for this are complex. Patients are known to have reduced levels of clotting factors Proteins C and S, as well as Factor VII [20, 21] and there is recent evidence to suggest that increased liver stiffness may further increase the clotting risk [19].

Therefore, thromboembolic events could theoretically be expected to increase in pregnant Fontan patients and events have been reported in these pregnancies but the numbers are small and it is difficult to draw any conclusions from the existing published data [19].

What is important though is that these patients are generally anticoagulated for the reasons above and to facilitate forward flow. We know that bleeding complications in

Fontan pregnancies are high, as described below, and thought needs to be given to the balance of bleeding and clotting in Fontan pregnancies. Whether to use antiplatelet agents or low molecular weight heparins, and at what dose, are all unanswered questions.

Obstetric complications

The most common obstetric complication in women with a Fontan circulation is bleeding. Where it has been documented, most women are either fully anticoagulated or treated with antiplatelet agents [15]. Haemorrhage has been reported in women who were not given any anticoagulant or antiplatelet but the numbers are small and bleeding in pregnancy is common and so it is difficult to draw conclusions from this. It seems logical though that the high risk of bleeding is largely due to the anticoagulation.

Both antepartum and postpartum haemorrhage are common. Antepartum haemorrhage is a consistent finding in a few patients per published study, reported as approximately 11% overall [15] but it has been reported in as many as 23% patients [22]. Post-partum haemorrhage, however, is a bigger problem and a recent large UK study found that it occurred in 43% of deliveries and more importantly, major haemorrhage (>two litres) occurred in seven women (14%) [21] (Table 1).

FOETAL complications

Foetal outcomes are extremely poor in the Fontan and this has been described by multiple authors in different countries. The live birth rate has been consistently reported as 40–50% [18, 19, 22] or even less [23].

Both first and second trimester miscarriage is common, reported in 27–69% of cases [13, 19, 22–24] and in those foetuses that survive, neonatal death is not uncommon, occurring in up to 5% live births [15]. This is likely to be due to prematurity in many cases, which affects up to 70–80% live births [11, 13, 19, 22].

Initial reports suggested that prematurity was not necessarily to be expected, with a reported mean gestational age in one study of 36.5 weeks [10]. However, since then, the evidence points to prematurity being the rule with median gestational age in a recent meta-analysis being 32 weeks [15, 25–27]. Premature rupture of membranes occurs in at least 10% cases [11, 13, 19], some have reported up to 20% [28]. Additionally, the rate of preterm labour is higher than in a normal pregnancy.

Poor foetal growth is common and the occurrence of small for gestation age (SGA) babies is the norm. Evidence reported SGA in up to 60% live births with the median birthweight being on the 9th centile [22, 28]. Furthermore, rates of intra-uterine growth retardation (IUGR) of 70% have been reported [22].

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, adverse hemodynamics including limited cardiac output, neurohormonal environment of the Fontan circulation, maternal medication (e.g. β -blockers), and iatrogenic prematurity. We know that maternal cyanosis is a risk factor for miscarriage. Although foetal haemoglobin is extremely efficient at extracting oxygen, once saturations are less than 85% the chances of a live birth are as low as 12% [28, 29]. This has been specifically reported in the Fontan population. A recent large multi-centre UK study with the largest pregnancy Fontan cohort in the literature of 124 pregnancies described miscarriage in all eight women in their cohort with oxygen saturations less than 85%, compared to 60 out of 116 (51.7%) who had baseline saturations of $\geq 85\%$ [28].

However, most women with a Fontan circulation are not cyanosed and clearly, some women do well. The reasons for this are poorly understood. We can assume, as with cirrhosis, that an adverse uterine environment exists, but we do not know which factors in particular are most harmful to the foetus. Therefore it is extremely difficult to counsel women with a Fontan circulation, aside from describing the known high foetal risks, and no reliable way to avert a poor foetal outcome when it presents in utero.

The placenta is a poorly studied area in this patient group. We recently described a case of a poor outcome in pregnancy in a 'good' Fontan patient, where the placenta was highly abnormal [30]. A small case series [31] has described a variety of placental abnormalities in this patient group, which needs further study and may provide further insights.

It must be borne in mind that, in the case of foetal demise, both surgical removal of the products of conception and delivery of a non-viable foetus are not without risk. Similarly, patients who become pregnant unintentionally and opt for therapeutic termination (7–9% reported cases) [15] will require a surgical procedure, again not without risk (Table 1).

Clinical management of the pregnant FONTAN

Pre pregnancy and estimating risk in the individual patient

Pregnancy carries varying risks in women with congenital hearts defects even after successful repair. Preconception evaluation is essential for genetic consultation, identifying potential medical and surgical issues before pregnancy in order to improve outcomes [24].

In the case of the Fontan circulation, women are aware from an early age that they have a significant heart problem but have not always had detailed pre-conception counselling. Contraception and pregnancy discussions

should be initiated prior to conception and ideally during teenage years. Though there is some evidence that menarche is delayed in Fontan patients [32, 33], it is important that these discussions are had early, as part of transition, and prior to transferring care from paediatric to adult services.

Such stratification is based on two elements: (a) maternal risk and (b) foetal risk [12]. Current risk calculators such as CARPREG, ZAHARA and the modified WHO criteria either do not include women with a Fontan circulation, or simply classify them as “high risk”. The CARPREG classification includes women with both acquired and congenital heart disease and assigns a point for each predictor (i.e. prior cardiac event, NYHA functional class >II or cyanosis, left heart obstruction, left ventricular ejection fraction < 40%). A score of 1 confers 27% risk of maternal cardiovascular complications and a score > 1 confers a 75% risk [15]. The ZAHARA study also identified predictors of adverse maternal events in patients with congenital heart disease [11]. The modified WHO criteria include specific cardiac lesions in addition to clinical cardiac status. It applies to women with acquired as well as congenital heart disease and the risk categories range from low risk (group I) to very high risk (group IV) [28, 29].

A thorough assessment of the Fontan should be done by echocardiography, cardiac magnetic resonance imaging (CMR) and cardiac catheterisation, as well as a biochemical and ultrasound assessment of the liver. Objective exercise data is also useful [25, 34]. If there are any complications, such as cyanosis (oxygen saturations below 90%), reduced ventricular function, atrioventricular valve regurgitation, arrhythmia history, raised Fontan pressure, protein-losing enteropathy, or thromboembolism, pregnancy should be avoided.

If pregnancy is deemed feasible (albeit high risk), each patient must be individually counselled as to the potential maternal and foetal risks for her, alongside sensitive counselling around parenting beyond infancy in the context of a severe life-limiting heart condition. One encouraging point is that, at this stage, there is no evidence that pregnancy results in deterioration of the clinical status of the Fontan up to 24 months post-partum [18, 19] and that maternal death has not been reported.

One tool that has been recently explored in the context of clinical consultations of CHD patients and parents of children with CHD is the use of patient-specific 3D printed models, to better elucidate aspects of the anatomy [27, 35, 36]. This could be particularly useful for Fontan patients in light of their unique vascular arrangement post Fontan repair, but it has not been systematically evaluated with pregnant Fontan patients. The feasibility of introducing these tools to this group of patients depends on the availability of suitable cross-

sectional imaging (i.e. three-dimensional datasets from either cardiovascular magnetic resonance imaging or computed tomography) providing the necessary input data for model making.

Occasionally, intervention pre-pregnancy can be performed in an attempt to improve foetal outcomes, such as collateral occlusion in the case of cyanosis. Medication needs to be reviewed as to whether or not it is safe for the foetus. Patient can be advised that anticoagulation can be continued but that it will be injectable in the form of low molecular weight heparin, rather than oral coumadins. Aspirin can be continued.

Arif et al. have proposed a new risk stratification model for pregnant women with a Fontan circulation [24] (Table 2). It includes predictors of poor clinical outcomes in the Fontan and data from the modified WHO criteria, which is considered to be the best available pregnancy risk calculator in women with congenital heart disease [23, 24, 27, 35] (Table 1). Though this model was created with 55 pregnancies in 21 women, only 13 fetuses were live born. There were more live births in the ‘lower risk’ group compared to the ‘very high risk’ group but this did not reach statistical significance (OR 7.60, 95% CI 1.81–31.97, $p = 0.06$), potentially due to the low number of live births. As the only method currently available to risk stratify these women, this model certainly warrants further validation [24].

Management and risk reduction during pregnancy

Multidisciplinary team management with good communication is the key to reducing complications in women with heart disease [27]. The team should involve maternal-foetal medicine specialists, cardiologists with expertise in congenital heart disease and pregnancy, obstetric anaesthetists, haematologists, and specialist midwives. Women should be managed as outpatients in a joint clinic with all specialists and required investigations being available in a one-stop setting.

Women need to be seen on a two to four weekly basis throughout pregnancy, increasing to weekly as the pregnancy progresses. A clinical assessment, electrocardiogram and echocardiogram need to be done at each visit, as well as careful foetal surveillance. A full blood count, liver function tests, urea and electrolytes, and brain natriuretic peptide (BNP) need to be done at least once per trimester.

Medication needs to be reviewed at booking. The role of anticoagulation during a Fontan pregnancy remains unclear. Though anticoagulation is definitely indicated in the presence of atrial thrombus, atrial arrhythmia or history of thromboembolic events [27], the evidence for its benefit in an otherwise uncomplicated Fontan, as mentioned above, is limited.

Table 2 Proposed risk stratification model for pregnant women with Fontan circulation. Women were classified into lower, intermediate and very high risk. Women were allocated to “intermediate” or “very high risk” groups based on achieving ≥ 1 criteria for that group. Adapted from [19]

	Lower risk	Intermediate risk	Very high risk
NYHA class	I	II	III-IV
SaO ₂ %	$\geq 94\%$	90–93%	< 90%
mVO ₂ (ml/kg/min)	> 60%	50–60%	< 50%
Systemic ventricular function impairment	none	mild	Moderate/severe
AVVR	none/mild	moderate	Severe
Fontan related complications	none	none	At least one
Failing Fontan	no	no	Yes

AVVR Atrioventricular valve regurgitation, mVO₂ Maximal oxygen uptake, NYHA New York Heart Association, SaO₂ Oxygen saturations

There is however a real risk of bleeding, as described above, and anticoagulation has been associated with an adverse neonatal outcome [19] (OR = 10.0, 95% CI [1.5–91.4], $p < 0.01$), as well as the risk to the mother from haemorrhage. Some authors have recommended prophylactic anticoagulation by low-molecular-weight heparin (LMWH) in patients with low thromboembolic risk, and therapeutic anticoagulation by LMWH in women with high thromboembolic risk (i.e. past history of arrhythmia or thromboembolic event) but with no real evidence to back up this recommendation [6].

If complications occur, these should broadly be treated as for any woman who is not pregnant, with a few caveats. For example, supraventricular arrhythmias should be treated in the usual way in the Fontan, with a low threshold for cardioversion in cases of sustained arrhythmia. Patients need to be kept hydrated if cardioversion is delayed. β -blockers can be used for arrhythmia prevention, although they result in an increased risk of IUGR in an already compromised foetus [28]. Full anticoagulation is recommended if not already in place.

Heart failure management in complex congenital heart disease should be individualised [6]. Angiotensin-converting-enzyme (ACE) inhibitors and angiotensin receptor blockers are contraindicated in pregnancy but β -blockers, alpha-blockers and nitrates can be used as well as loop diuretics. Deterioration of ventricular function however usually prompts delivery of the foetus for the sake of the mother’s health and post-partum any drugs can be used, though care should be taken with regard to their excretion into breast milk. As always in obstetric cardiology, if the mother’s life is at risk, the best available treatment should be instigated with secondary consideration being given to the foetus.

Delivery should be planned early, given the high risk of foetal demise, but clearly extreme prematurity should be avoided if possible. Vaginal delivery is the aim with a carefully titrated epidural and assisted second stage but, due to the need for premature delivery, Caesarean section has been required in 60–80% cases [19, 22, 28]. A

senior team needs to be involved from an anaesthetic and obstetric point of view. There should be a low threshold for invasive monitoring.

Large boluses of intravenous fluid should be avoided but patients need to be kept well hydrated to maintain left atrial pressure. Ergometrine should be avoided in the third stage and any haemorrhage treated promptly but carefully.

Management post-partum

The post-partum period is associated with an additional haemodynamic challenge as the uterine blood is auto-transfused back into the circulation and the direct pressure on the inferior vena cava from the mass of the baby is relieved. This 48–72 h period after delivery is a time of increased risk in women with heart disease and often when cardiac events occur, particularly in those at risk of ventricular decompensation.

Fontan patients should remain in an intensive care environment for at least 24–48 h after delivery. Careful fluid balance, heart rate and blood pressure monitoring are essential during this time [26, 27].

A comprehensive echocardiographic assessment should be performed before discharging the patient from hospital, looking at the Fontan conduit flow, presence of thrombus, atrioventricular valve and single ventricle function. Thromboembolic prophylaxis should be continued at least for 6 weeks after pregnancy. Therapeutic anticoagulation should be restored, based on centre policy, once any post-partum bleeding has settled. Continuing low molecular weight heparin for several weeks is a good way of avoiding severe haemorrhage after delivery, which can be unpredictable and difficult to manage on oral anticoagulation therapy.

New insights

In addition to recent advances in medical imaging, such as 4D MRI that is proving to be particularly insightful in Fontan patients [35–37], one tool that could potentially shed light into the mechanisms of hemodynamic

adaptation to pregnancy in a complex circulation such as the Fontan is computational modelling. Computational models, in the form of computational fluid dynamics (CFD) or multiscale/multiphysics simulations have been used for many years in the context of evaluating the Fontan circulation. Indeed, probably because of the complexity of the Fontan anatomy and its unique fluid dynamics, modellers have been studying flow distribution in the total cavopulmonary connection (TCPC) since the 1990s [35].

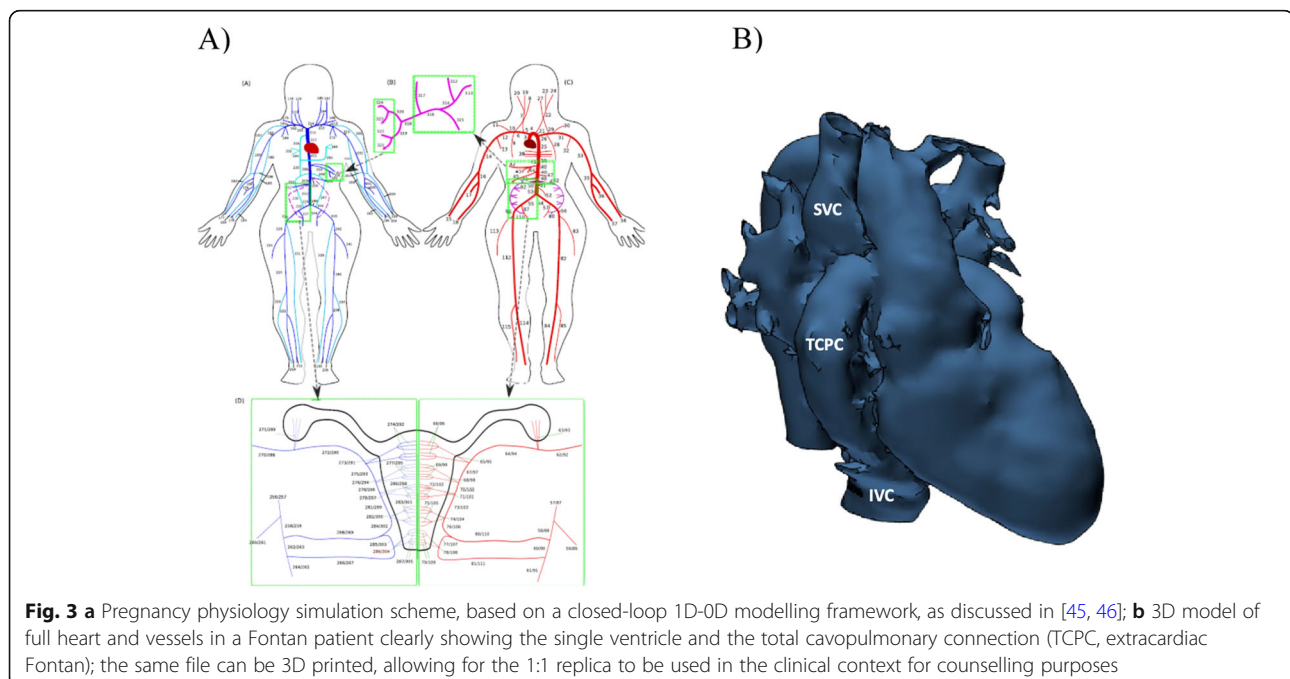
Computational modelling has been used to evaluate different aspects of the Fontan circulation at all stages of palliation, including flow distribution in different TCPC configurations, the hybrid Norwood circulation [38], changes in coronary perfusion [38] and virtual surgery to address pulmonary arteriovenous malformations in Fontan patients [39]. It has also been used for exploring innovations for the surgery itself including the Y graft baffle for Fontan completion, the assisted bi-directional Glenn and a physiological Fontan connection [39–42].

Computational models, including lumped-parameter models, of the Fontan physiology can also be used to simulate exercise and test the physiological impact of the typical dysfunction that occurs in these patients [43, 44]. Finally, computational models have also been used to explore pregnancy physiology [45, 46], including studying utero-ovarian blood flow and uterine hemodynamics, including pulsatility indices (Fig. 3).

Whilst, to our knowledge, a full computational model of the Fontan circulation during pregnancy has not yet

been described, computational methodologies certainly hold potential for performing parametric studies and predictive simulations, ultimately generating new insights into this complex physiological scenario. This also extends to modelling the imaging data that can be gathered clinically, as in the case of a study that performed principal component analysis based on flow curves derived from the MRI scans of paediatric patients who underwent single ventricle palliation culminating in a Fontan procedure, describing a relationship between the diastolic flow variations in the pulmonary arteries and the single ventricle function and volumes [47]. Reduced-order modelling can also play a role in this context, as in the case of a biomechanical closed-loop model of the heart coupled with a simplified circulation allowing to perform patient-specific simulations and studying parameters such as myocardial stiffness, contractility at rest, contractile reserve during stress and changes in vascular resistance, providing insights into the pathophysiological response to stress in Fontan patients [48]. As in the above-mentioned case (Kung et al.), such simulations of exercise response can be important also in the context of pregnancy physiology, in light of the fact that pregnancy can be considered as a “stress test” to a woman’s cardiovascular system [49].

Refining computational modelling of both the Fontan circulation and pregnancy can hold promise to increase the understanding of a complex physiology adapting under stress, including the uterine environment and factors mentioned earlier e.g. variations in portal pressures and IVC compression.



Conclusion

There are a number of unanswered questions with regards to pregnancy in the Fontan. We still don't know quite why the foetus has such a poor outcome, both in terms of foetal loss and poor growth and also why some foetuses have a much better outcome than others. We do not fully understand the complex relationship between the foeto-placental unit, the Fontan and the liver and what maternal factors are most important (for example type of Fontan, function of ventricle and so on). We do not know the role of anticoagulation but given the high risk of haemorrhage, both antepartum and postpartum, consideration needs to be given to whether or not this ought to be given during pregnancy and at what dose. We need to know how to best counsel an individual woman about her risk, and how it might be reduced.

Further study of the placenta in Fontan patients and collaborations between cardiologists and bioengineers in designing a computational model of the pregnant Fontan, may help to answer some of these questions.

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