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The placenta: A site of end-organ damage after Fontan operation. A case series

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ABSTRACT

Background: Placental insufficiency may be the cause of the high preterm birth rate in women after Fontan operation. In this study we reviewed the clinical course and pregnancy outcome of women with Fontan physiology with a focus on placental pathology.
Methods: We reviewed clinical charts and placental pathology from 7 women with Fontan physiology who had pregnancies at Mayo Clinic, Rochester, Minnesota. The review was limited to cases where placental pathologic specimens were rigorously examined.
Results: Seven women had 13 deliveries between 2002 and 2018. Only 2 of 13 deliveries were at term (>37 weeks). Mean maternal age at time of last delivery was 27.5 ± 3.2 years. Preeclampsia was noted during 2 pregnancies and 2 women had preterm premature rupture of membranes at 24 and 35 weeks gestation, respectively. Placental abruption with bleeding occurred in 2 pregnancies. An additional 4 pregnancies were complicated by intrauterine growth restriction (IUGR). Median placental weight was 441.5 g (IQR 305.5–622.5 g). Median placental weight percentile for gestational age was 10th to 25th, but varied greatly; two placentas were <10th percentile and 5 were >90th percentile for gestational age. Two umbilical cords contained a single umbilical artery. Prominent subchorionic fibrin deposition was a consistent feature in all placentas. Villous hypermaturity was noted in 4 placentas.
Conclusions: Fontan physiology may be associated with poor placental health. High systemic venous pressure and low cardiac output may contribute to stagnation of placental blood flow and result in subchorionic fibrin deposition and variable villous hypoplasia. This may explain the high preterm birth rate in women with Fontan physiology. Preterm deliveries and small-for-gestational-age (SGA) newborns should be anticipated in this patient population. Analysis of placental pathology may help determine both candidacy for future pregnancy and long-term effects of pregnancy for women with Fontan physiology.

1. Introduction

Since the early 1970s, the Fontan operation has served as definitive palliation for thousands of patients with functional single ventricle physiology. Survival for 30+ years after Fontan has been reported [1]. While overall survival has improved, the physiology of Fontan flow contributes to long-term problems with other organ systems, including progressive hepatic disease and protein losing enteropathy. The rigors of pregnancy may prove difficult for women with Fontan physiology [1,2]. Several investigators have evaluated post-Fontan pregnancy outcomes and all describe relatively high obstetrical complication rates (>50%) with many pregnancies resulting in preterm, low birth weight or small-for-gestational-age (SGA) newborns [3–6]. Placental insufficiency may contribute to the high preterm birth rate in women with Fontan physiology.

Placental insufficiency may be associated with miscarriage, fetal growth restriction, oligohydramnios, preeclampsia and stillbirth. The deleterious effects of preeclampsia-related systemic hypertension coupled with hypovolemia and low cardiac output from Fontan physiology may ultimately cause placental insufficiency. Similar to the liver, the placenta appears to sustain end-organ damage from the Fontan state of hypovolemia [7–9].

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In this case series we reviewed the clinical course and pregnancy outcome of several women with Fontan physiology. The focus of the review was limited to pregnancies in which the placenta had undergone rigorous histopathologic examination.

2. Materials and methods

We retrospectively reviewed clinical charts and placental pathology from 7 women with Fontan physiology who had pregnancies at Mayo Clinic, Rochester, Minnesota between November 2002 and July 2018. Although more women with Fontan physiology had pregnancies at our institution during this time interval [3], only this subset of placentas had request for formal pathology examination. These were nonconsecutive cases and all were live born deliveries. Placentas were not selected for pathologic evaluation based on clinical suspicion or poor pregnancy outcome.

3. Results

3.1. Maternal data

Thirteen placentas from 7 women were subject to pathologic evaluation after deliveries. Four women had 1 pregnancy, one had 2, one had 3, and one woman had 4 successful pregnancies. Mean maternal age was 27.5 ± 3.2 years. The oldest mother was 33 years old. Fontan operations were performed at a mean age of 8.6 ± 7.3 years. These women had 1–3 surgeries prior to Fontan. Four women were taking cardiac medications at the time of delivery (digoxin, beta-blocker or a diuretic). Six women were anticoagulated during the pregnancy with aspirin and 1 with low molecular weight heparin. These women were hospitalized from 0 to 67 days prior to delivery (the 67 day hospitalization was due to preterm premature rupture of membranes) and 1 to 7 days postpartum, with at least the first postpartum day in an intensive care unit per our institution's practice. All women were alive at the time of this review, 0–16 years after first delivery and 0–7 years since most recent delivery.

3.2. Maternal cardiac data

Supraventricular tachycardia occurred in 2 women during pregnancy. Systemic hypertension was noted in 2 patients. All 7 women had lateral tunnel type Fontan connections. Four women had left ventricular morphology (2 tricuspid valve atresia, 1 double inlet left ventricle, 1 pulmonary valve atresia with intact ventricular septum) and 3 women had right ventricular morphology (1 unbalanced atrioventricular septal defect, 2 double outlet right ventricle with mitral valve atresia). There was 1 patient with heterotaxy (asplenia).

Two women had pacemakers prior to pregnancy. Two women had Fontan-associated liver disease (FALD) at time of pregnancy. None had protein-losing enteropathy. Ventricular ejection was ≥40% and ambient systemic arterial oxygen saturation was ≥89% in all.

3.3. Newborn data

All neonates (3 female, 10 male) were born alive. All pregnancies were singleton and median gestational age at time of delivery was 35.4 weeks (IQR 31.1–36.5 weeks). Only two deliveries were at term (>37 weeks). Median birth weight was 2.210 kg (IQR 1.037–2.732 kg) and 62% (8/13) were appropriate-for-gestational-age (AGA), 31% (4/13) were SGA, and 1 (8%) was large-for-gestational-age (LGA). One newborn had single ventricle physiology complicated by obstructed total anomalous pulmonary venous connection and did not survive neonatal cardiac surgery. The other 12 newborns survived to hospital discharge and were alive at the time of this review.

3.4. Obstetrical data

Preeclampsia developed in 2 pregnancies. Two women had preterm premature rupture of membranes at 24 and 35 weeks gestation, respectively. Placental abruption with bleeding occurred in two women. An additional 4 pregnancies were complicated by fetal IUGR.

3.5. Placental pathology

Median placental weight was 441.5 g (IQR 305.5–622.5 g). Median placental weight for gestational age was 10th to 25th percentile. However, the range varied widely with two placentas weighing less than 10th percentile and 5 greater than the 90th percentile. Subchorionic fibrin deposition was prominent during microscopic examination and on

Fig. 1. Pathologic specimen of a 32-week placenta with extensive fibrin deposition from a 30 year old woman with unbalanced atrioventricular septal defect (a). In comparison to the pathology demonstrated in panel a, maternal surface (b) and fetal surface (c) from a normal placenta.

gross examination it was extensive and thick (Figs. 1, 2). Associated circummargination of part of the fetal membrane insertion was described in 4 cases. Abruption with retroplacental hematoma was documented in one placenta delivered at 29 weeks. A variable degree of villous hypoplasia was present in 4 placentas and most severe in one woman with preeclampsia who delivered at 36 weeks (Fig. 3). No maternal vasculopathy was observed in any of the cases, although decidual sections were limited.

4. Discussion

As Rychik et al., stated in their report of placental pathology in newborns with congenital heart disease; "The human placenta … is a complex and highly structured organ … it is the only human organ than can be grown as new, discarded, then de novo grown again" [10]. Unfortunately this led to less rigorous pathologic evaluation of placentas, especially in women with congenital heart disease. Hopefully our case series and the study from the Children's Hospital of Philadelphia group will challenge this practice.

Cardiac output in patients with Fontan physiology is dependent on elevated preload and filling pressures. Any obstruction to flow in the vascular pathway will create serious hemodynamic problems. Increased central venous pressure in the abdomen is an obligate consequence of Fontan physiology. In addition, some patients after Fontan operation have a relatively low cardiac output. These patients have limited reserve to increase cardiac output to match physiological needs [7].

For these reasons, the rigors of pregnancy may prove difficult for women with Fontan physiology. The baseline physiology of patients after Fontan operation is important when anticipating pregnancy. The limited studies that are available regarding post-Fontan pregnancy outcomes list relatively high obstetrical complication rates (>50%) and many of these pregnancies resulted in preterm, low birth weight or SGA newborns [11]. In 2015, the Mayo Clinic reported that the preterm birth rate for women who had pregnancies after Fontan was 81% [3]. Similarly, in a recent French study, the preterm birth rate was 69% [4]. In both studies, the mean birth weight of all newborns was only 2.0 kg.

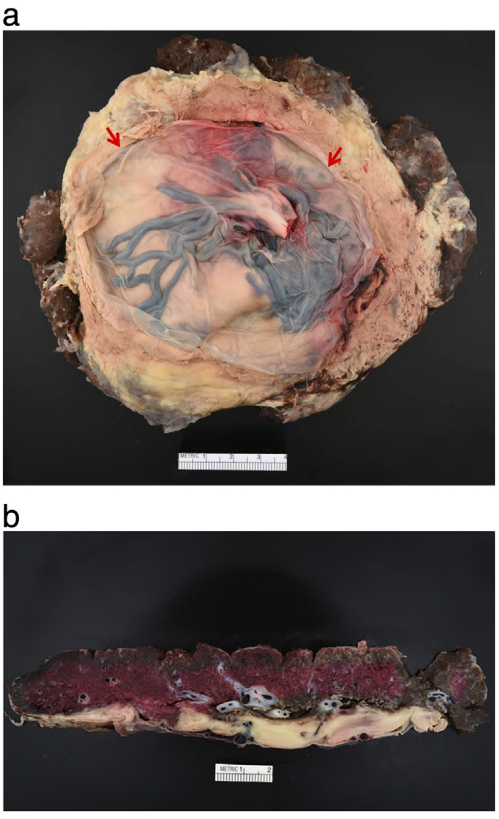

Fig. 2. a. Pathologic specimen of a 35-week placenta with typical findings observed in women with Fontan physiology. Extensive subchorionic fibrin deposition is seen on the fetal surface. The fetal membranes demonstrate a circumvallate insertion (arrows). b. Cross-section of the pathologic specimen displayed in panel a showing extensive subchorionic fibrin deposition.

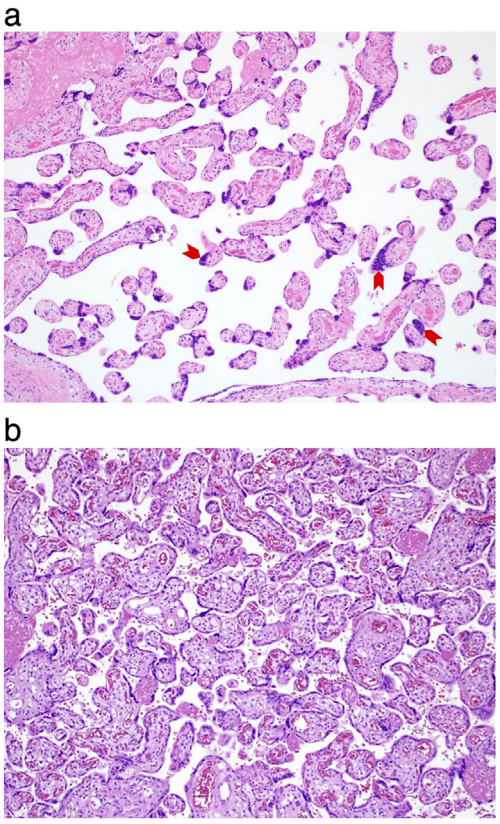

Fig. 3. a. Histology of placental chorionic villi from a 36-week placenta from a 31 year old woman with Fontan physiology. The pregnancy was complicated by preeclampsia and intrauterine growth restriction (H&E, 100× magnification). The small size and uniformity of the terminal villi with associated increased syncytial knots (arrows) are known as "villous hypoplasia". b. In comparison to the pathology demonstrated in panel a, normal chorionic villous histopathology of a 36-week placenta (H&E, 100× magnification).

Placental insufficiency may cause oligohydramnios, preeclampsia, miscarriage or stillbirth [12–16]. Placental insufficiency is considered the most frequent cause of asymmetric IUGR. Many women following Fontan operation may have relatively low arterial oxygen saturation. In the previous Mayo Clinic study, only women with systemic arterial saturations ≥90% experienced successful pregnancies [3]. Hypoxemia is known to cause villous changes in the placenta which include adaptive and maladaptive changes (villous hypoplasia with increased syncytial knots; chorioangiosis) or injury (infarction). In turn, maternal hypoxemia may lead to fetal hypoxemia. Interestingly, these placental hypoperfusion changes were most prominent in a subset of the cases in this series in the women with preeclampsia.

Prominent subchorionic fibrin deposition was a more consistent feature of the placentas examined in this study. It was associated with abnormal circummarginate fetal membrane insertion in some cases. Subchorionic fibrin deposition normally increases with gestational age and is usually attributed to the more sluggish venous return of late pregnancy. Circummargination of the membranes often is associated with placental abruption and was clinically suspected in two cases in this series. This combination of features is unique. Fontan physiology may be associated not only with preeclampsia and hypoxemia in some cases, but also may be more consistently associated with substantial venous resistance leading to chronic small abruptions and stagnation of

placental blood flow. This may result in the subchorionic fibrin deposition seen in this series. While subchorionic fibrin did not significantly displace or entrap the villi, subchorionic fibrin could lead to underperfusion of the fetus by compression of the chorionic and larger stem vessels leading to IUGR.

The deleterious effects of subchorionic fibrin deposition coupled with hypoxemia and relative low cardiac output of Fontan physiology ultimately may cause placental insufficiency, preeclampsia and foreshadow long-term deleterious cardiovascular health concerns for the mother [17]. Recent reviews of women with other forms of congenital heart disease demonstrated that insufficient cardiac output during pregnancy may be a common issue [18,19]. More study is required regarding the pathology of the placenta in women with Fontan physiology. It may be that, similar to the liver, the placenta represents another site of end-organ damage.

5. Conclusions

Fontan physiology may not be compatible with good placental health. Chronic hypoxemia, high systemic venous pressures and low cardiac output likely contribute to poor placental physiology. This may explain the high preterm birth rate in women with Fontan physiology. That said, select women after Fontan operation can have successful pregnancies. However, for these women, preconception counseling, cardiology and obstetrical evaluation, peri-partum care and follow-up need to be meticulous. Preterm deliveries and SGA newborns should be expected. Maternal-fetal medicine specialists, neonatologists and cardiologists need to plan accordingly.

The most important questions confronting women considering pregnancy after Fontan are: 1) whether the hemodynamic stress of pregnancy will compromise maternal quality of life and/or longevity? and 2) what is the probability of a favorable neonatal outcome? In the next decade these questions need to be addressed as more women with Fontan physiology enter their reproductive timeframe. Evaluation of placental pathology may enhance our knowledge of the effects of Fontan physiology on neonatal outcomes.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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