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Delivery trends and obstetric outcomes in patients with Fontan circulation



Nasim C. SOBHANI MD MAS ,
Chiara M. CORBETTA-RASTELLI MD , Anushree AGARWAL MD ,
Mary E. D'ALTON MD , Alexander M. FRIEDMAN MD MPH ,
Timothy WEN MD MPH

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Title: Delivery trends and obstetric outcomes in patients with Fontan circulation

Authors: Nasim C. SOBHANI MD MAS^a, Chiara M. CORBETTA-RASTELLI MD^a, Anushree AGARWAL MD^b, Mary E. D'ALTON MD^c, Alexander M. FRIEDMAN MD MPH^c, Timothy WEN MD MPH^a

Affiliations

^a Division of Maternal Fetal Medicine, Department of Obstetrics, Gynecology, and Reproductive Sciences, University of California San Francisco

^b Division of Cardiology, Department of Medicine, University of California San Francisco

^c Division of Maternal Fetal Medicine, Department of Obstetrics and Gynecology, Columbia University Irving Medical Center

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Corresponding author: Nasim C. Sobhani, MD MAS | Nasim.Sobhani@UCSF.edu

490 Illinois Street, 10th Floor, San Francisco, CA 94143 | 415-613-4462

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Condensation: Deliveries among patients with Fontan circulation are increasing nationally and are associated with ~2-6-fold higher rates of obstetric complications and severe maternal morbidity.

Short Title: Pregnancy with Fontan

AJOG at a Glance:

A. Why was this study conducted?

- To use nationwide data to evaluate temporal trends in deliveries to gravidas with Fontan circulation and to estimate absolute and relative risk of obstetric complications.

B. What are the key findings?

- The rates of Fontan deliveries increased more than 12-fold over the 18-year period examined in this serial cross-sectional study.
- Although Fontan deliveries are associated with a 6-fold increase in the risk of severe maternal morbidity, the absolute risk of this composite outcome is < 10%.

C. What does this study add to what is already known?

- Cardio-obstetric providers should be prepared for an increasing number of pregnant Fontan patients and should understand the magnitude of increased complications in order to appropriately counsel and care for these patients.

Keywords: univentricular physiology, congenital heart disease, cardio-obstetrics, pregnancy perinatal outcomes, obstetric complications

Abstract

Background: With improved therapies, an increasing number of patients with Fontan circulation reach reproductive age. Pregnant patients with Fontan circulation are at high risk for obstetric complications. Most data for Fontan pregnancies and associated complications stem from single center studies, with limited national epidemiologic data available.

Objective: To evaluate temporal trends in deliveries to pregnant individuals with Fontan palliation using nationwide data and to estimate associated obstetric complications among these deliveries.

Study design: Delivery hospitalizations were abstracted from the 2000-2018 Nationwide Inpatient Sample. Fontan deliveries were identified using diagnosis codes and trends in the rates of these deliveries were assessed using joinpoint regression. Baseline demographics and obstetric outcomes (including severe maternal morbidity (SMM), a composite of serious obstetric and cardiac complications) were assessed. Univariable log linear regression models were fit comparing risks of outcomes among deliveries with and without Fontan circulation.

Results: 509 pregnancies complicated by Fontan circulation were identified at a rate of 7 per 1 million delivery hospitalizations, with a temporal increase from 2.4 to 30.3 cases per 1 million from 2000 to 2018 ($p < 0.01$). Compared to non-Fontan deliveries, Fontan deliveries were at higher risk of hypertensive disorders (RR 1.79, 95% CI 1.42-2.27), preterm delivery (RR 2.37, 95% CI 1.90-2.96), postpartum hemorrhage (RR 4.28, 95% CI 3.35-5.45), and SMM (RR 6.09, 95% CI 4.54-8.17).

Conclusions: The rates of deliveries to patients with Fontan palliation are increasing on a national level. These deliveries have higher risks of obstetric complications and SMM.

Additional national clinical data are necessary to better understand Fontan pregnancy complications, to improve patient counseling, and to reduce maternal morbidity.

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Introduction

Some complex congenital cardiac conditions are characterized by univentricular physiology, with only one functional ventricle to maintain both systemic and pulmonary blood circulation. The Fontan operation is typically the last in a series of cardiac procedures that are performed for surgical palliation of univentricular physiology.¹ This operation accomplishes a separation of systemic and pulmonary circulation, such that the single ventricle actively pumps oxygenated blood to the systemic circulation, while venous return travels passively into the pulmonary circulation without an intervening pump.²

There have been considerable improvements in cardiac care such that the early mortality related to the Fontan procedure has been significantly reduced.³⁻⁵ As a result, survival to adulthood is common, and many patients are now capable of reaching reproductive age and pursuing pregnancy. The normal physiologic changes of the antepartum and postpartum states place numerous stressors on the Fontan circulation, which is preload-dependent with a relatively fixed cardiac output and thus has limited capacity to tolerate pregnancy-related changes in plasma volume, cardiac output, stroke volume, systemic vascular resistance, and pulmonary vascular resistance.⁶ Consequently, pregnancy with Fontan circulation carries considerable obstetric and cardiac risks.⁷ Data regarding these risks in modern care arise primarily from case series,⁸⁻¹¹ single institution reports,¹²⁻¹⁴ and regional studies,^{15,16} with only one study providing nationwide data from 1998 to 2012.¹⁷ To address this gap, our group designed a serial cross-sectional study using a more recent nationally representative sample to explore temporal trends in Fontan deliveries and to identify the risk of obstetric complications associated with Fontan circulation.

Materials and Methods

Data source and patient population

Data were obtained from the 2000-2018 Nationwide Inpatient Sample (NIS) from the Agency for Healthcare Research and Quality's Healthcare Cost and Utilization Project.¹⁸ The NIS is one of the largest publicly available, all-payer inpatient databases and includes over 7 million hospitalizations annually, representing a 20% stratified sample of all hospitalizations in the United States. Hospitalizations in the NIS can be weighted to calculate national estimates that are representative of the entire population; specific NIS weights for trends were applied in this study.¹⁹ In 2015, national coding switched from the Ninth Revision of the International Classification of Diseases (ICD-9-CM) to the Tenth Revision (ICD-10-CM). As a result, billing data from the 2000-2018 NIS are in the form of both ICD-9-CM and ICD-10-CM codes.²⁰ Both codes were included in this analysis, with ICD-9-CM codes translated to ICD-10-CM codes using the publicly available General Equivalence Mappings provided by the Centers for Medicare and Medicaid Services and the National Center for Health Statistics.^{21,22} Delivery hospitalizations from 2000 to 2018 to women aged 15 to 54 were identified using ICD-9-CM and ICD-10-CM codes as previously described.^{23,24}

Definitions

Presence of Fontan circulation was identified using diagnosis codes of tricuspid atresia, hypoplastic left heart syndrome, or common ventricle (Appendix 1), an approach that has been previously utilized to identify adult patients with Fontan circulation.²⁵⁻²⁷ Baseline patient and hospital characteristics were derived from the NIS and included advanced maternal age (dichotomized as ≥ 35 years and < 35 years, based on the definition commonly used in obstetric practice), maternal race/ethnicity, obesity (defined as body mass index ≥ 30 kg/m²), year of

delivery, patient payer status, median income quartile by ZIP code, hospital region (Northeast, Midwest, South, or West), and hospital teaching status (urban teaching, urban non-teaching, or rural). Obstetric outcomes of interest were obtained from diagnosis codes (Appendix 1) and included preterm delivery (delivery < 37 weeks gestation), hypertensive disorders of pregnancy (HDP, including gestational hypertension and preeclampsia), antenatal bleeding (including placental abruption and antenatal hemorrhage), cesarean delivery, postpartum hemorrhage (PPH), transfusion of blood products, postpartum infection, and severe maternal morbidity (SMM). SMM is a composite measure defined by the Centers for Disease Control and Prevention that includes unexpected obstetric outcomes with significant short- and/or long-term implications for health.²⁸ Individual components of SMM are identified by ICD-9-CM or ICD-10-CM codes and include acute myocardial infarction, cardiac arrest, conversion of cardiac rhythm, heart failure, thrombotic embolism, temporary tracheostomy, ventilation, shock, and sepsis.²⁹ SMM is a well-studied grouping of adverse conditions and procedures used within the obstetrics literature.³⁰ SMM was also divided into non-cardiac SMM and cardiac SMM for analysis.

Statistical analyses

Differences in patient and hospital characteristics in Fontan deliveries versus non-Fontan deliveries were compared using the standardized mean difference (SMD), with SMD > 10% considered a clinically important difference between the groups.³¹

The first objective of this study was to describe national temporal trends in delivery hospitalizations with Fontan circulation. For this objective, we calculated the annual number of deliveries with Fontan circulation per 1 million delivery hospitalizations from 2000 to 2018. Trends in the rates of Fontan delivery hospitalizations were assessed using the Joinpoint

Regression Program (version 4.8.0.1) from the National Cancer Institute.^{32,33} This program uses linear segmented regression and logarithmic transformations to determine patterns in temporal trends and to test for statistical significance of apparent changes in trend. Measures of association are reported as annual average percent change (AAPC), which is the transformed, weighted average of the slope coefficients of the best fitting joinpoint regression line, with the weights equal to the length of each segment.^{32,34}

The second objective of this study was to analyze obstetric outcomes among deliveries with and without Fontan circulation. For this objective, we fit univariable log linear regression models comparing risks of obstetric complications between the two groups. Results were presented as unadjusted risk ratios (RR) with 95% confidence intervals (CI). Adjusted analyses were not performed due to the small number of outcomes in the Fontan group. These analyses were performed using SAS 9.4 (SAS Institute, Cary, NC).

The STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines for cross-sectional studies were followed for all analyses.³⁵ The senior author had full access to all the data in the study and takes responsibility for its integrity and the data analysis. This study was deemed exempt by the Institutional Review Boards at the affiliated study centers.

Results

A total of 73,109,791 delivery hospitalizations were identified in 2000 to 2018 and included in this analysis, with 509 complicated by Fontan circulation, for an overall rate of 7 cases per 1 million delivery hospitalizations. There was a temporal increase in the rate of Fontan deliveries from 2.4 cases per 1 million deliveries in 2000 to 30.3 cases per 1 million deliveries in 2018 (AAPC 19.3%, 95% CI: 10.9%, 28.3%) (Figure 1). Compared to those without Fontan

circulation, delivering patients with Fontan circulation were less likely to be of advanced maternal age (8% vs 15%) and more likely to be obese (12% vs 4%) (Table 1). Fontan deliveries were less likely to occur in those with private insurance (41% vs 52%) and more likely to occur at an urban teaching hospital (91% vs 51%).

Assessment of obstetric complications demonstrated consistent association between Fontan circulation and increased antepartum and postpartum complications (Figure 2, Appendix 2). Compared to non-Fontan deliveries, Fontan deliveries were more likely to be complicated by HDP (14% vs 8%, RR 1.79, 95% CI 1.42, 2.27), antenatal bleeding (5% vs 1%, RR 3.71, 95% CI 2.51, 5.48), and preterm delivery (16% vs 7%, RR 2.37, 95% CI 1.90, 2.96). Fontan deliveries were more likely to occur via cesarean than non-Fontan deliveries (41% vs 31%, RR 1.33, 95% CI 1.16, 1.53). In the postpartum period, Fontan deliveries had higher risks of PPH (13% vs 3%, RR 4.28, 95% CI 3.35, 5.45) and infection (RR 2.67, 95% CI 1.44, 4.96). Fontan deliveries were also associated with a higher risk of transfusion of blood products (RR 3.38, 95% CI 2.04, 5.60). Overall, risk of composite SMM was 6-fold higher in Fontan deliveries compared to non-Fontan deliveries (9% vs 1%, RR 6.09, 95% CI 4.54, 8.17). Fontan deliveries had a higher risk of both cardiac SMM (5% vs 0%, RR 9.85, 95% CI 4.75-16.85) and non-cardiac SMM (7% vs 1%, RR 5.60, 95% CI 4.02-7.80).

Discussion

Principal findings

The rates of delivery hospitalizations with Fontan circulation are increasing on a national level, with a more than 12-fold increase over the 18-year period examined in this serial cross-sectional study. Fontan deliveries are associated with significantly increased risk of obstetric

complications, including a 6-fold increase in severe maternal morbidity. These findings are not unexpected, given national trends in survival following the Fontan procedure and the known complex physiology of the Fontan circulation.

Comparison with existing literature

Many prior studies examining pregnancies complicated by Fontan circulation have been case series,⁸⁻¹¹ single center reports,¹²⁻¹⁴ or regional studies,^{15,16} with a wide range of reported obstetric complication rates in Fontan pregnancies. For example, the reported incidence of preterm delivery ranges from as low as 5%³⁷ to as high as 80%,¹⁴ and the reported incidence of cesarean delivery ranges from as low as 20% to as high as 72%.¹⁵ These disparate reports may be reflective of the imprecise estimates and selection bias associated with small sample sizes and speak to the value of nationwide studies.

One group has previously utilized the NIS to evaluate all pregnancy-related admissions to individuals with Fontan circulation from 1998 to 2012.¹⁷ Many of our findings are consistent with this prior publication, including a high proportion of Fontan hospitalizations occurring at a teaching hospital (77% and 91%) and a similar preterm delivery rate (18% and 16%). Despite the similarities in design and approach, our current study offers additional important insight. Notably, because 31% of hospital admissions included in the prior report were not delivery hospitalizations, only 194 delivery hospitalizations were available for assessment of ultimate pregnancy outcomes, which is considerably lower than our current sample size of 509. Due to the smaller sample size, the previous authors were unable to report absolute or relative risk of some obstetric complications, including HDP or PPH. Understanding the absolute and/or relative risk of these complications is particularly important in this population, since the hemodynamic derangements of HDP are poorly tolerated by individuals with pre-existing cardiac disease and

the hypovolemic sequelae of PPH can have serious consequences for the preload-dependent Fontan circulation.

Ultimately, our study adds to the existing literature by evaluating contemporary nationwide cohort of Fontan deliveries, by providing absolute and relative risks of multiple obstetric complications, including the important composite of SMM, and by reporting temporal trends in Fontan deliveries, which is critical for understanding perinatal epidemiology.

Clinical implications

This study identified a steady rise in deliveries to individuals with Fontan circulation over time, a trend that is only expected to increase as cardiovascular care continues to improve for these patients. In anticipation of this continuing trend, providers must ensure that they are well-versed in the physiology of Fontan circulation in pregnancy, the potential cardiac and obstetric complications, and the appropriate approaches to management in the antepartum, intrapartum, and postpartum periods. It is imperative that high-risk obstetricians understand the complex physiology of Fontan circulation and that cardiologists understand the unique physiologic challenges of pregnancy. A team-based approach to management of these patients is now considered standard of care, given the apparent improvements in outcome when pregnant patients with complex cardiac disease are cared for by a multidisciplinary cardio-obstetric service that is comprised of specialists in Maternal-Fetal Medicine, Cardiology, Obstetric and/or Cardiac Anesthesia, and Nursing.^{38,39}

This study also provides absolute and relative risks of obstetric complications that can be used clinically to improve counseling regarding obstetric risks to patients with Fontan circulation. Numerous cardiac classification schemes have been developed to guide counseling regarding cardiac risk in pregnancy, including the CARPREG score, the CARPREG II score, the

ZAHARA score, and the modified WHO risk classification.⁴⁰⁻⁴³ These cardiac scores provide valuable information regarding the risk of maternal cardiac events in pregnancy but do not provide information regarding the risk of obstetric events. The relative and absolute obstetric risks reported here can be incorporated into routine counseling provided by a multidisciplinary cardio-obstetrics team.

Importantly, these data should be reviewed with patients not only during pregnancy but ideally prior to pregnancy. Preconception consultation can improve outcomes in the congenital heart disease population and should be offered to all reproductive-aged women with Fontan circulation to allow for informed decision-making regarding personal family planning preferences. This type of consultation is generally well-accepted, with a prior study reporting that over 90% of patients with Fontan palliation accept preconception consultation when it is routinely offered.¹¹

Study limitations

When interpreting the results of this study, one must consider important limitations, many of which are inherent to studies that rely on administrative data. The use of a dataset built on ICD-9-CM and ICD-10-CM codes subjects this study to misclassification bias.⁴⁴ Because the NIS dataset samples cross-sectionally, it cannot track multiple deliveries in the same individual, and thus we cannot account of the possibility of correlated outcomes within an individual. The absence of granular clinical information available in the NIS dataset precludes the ability to comment on other important covariates and outcomes, including baseline status, cardiac function in pregnancy, echocardiogram changes, and neonatal outcomes. The dataset also prevents us from being able to provide clinical details driving increased complication rates, such as indications for cesarean delivery and etiologies of PPH. Similarly, because only delivery

hospitalizations were included in this study, we are unable to provide information regarding early pregnancy outcomes, including first trimester miscarriages, mid-trimester pregnancy loss, and termination of pregnancy. These types of pregnancy loss are known complications of Fontan circulation, with a prior systematic review reporting an overall pregnancy loss rate of 54%.⁴⁵ It is possible that a higher-risk subgroup of Fontan pregnancies was more susceptible to these early outcomes, thus leaving a biased sample of lower-risk Fontan pregnancies available for our analysis.

Conclusions

This analysis of national temporal trends demonstrated increasing rates of delivery hospitalizations with Fontan circulation, which are associated with increased risk of numerous obstetric complications and severe mortality morbidity. Coupled with previously published data regarding cardiac risks in pregnancy, these obstetric data provide valuable information for patients considering pregnancy and for cardio-obstetric clinicians caring for these complex patients. Additional national multicenter data with more detailed clinical information could help to better understand pregnancy complications, improve patient counseling, and reduce maternal morbidity in the growing population of pregnant individuals with Fontan circulation. Research efforts should also focus on evaluating the long-term effects of pregnancy on cardiac function later in life among these individuals, including a comparison of long-term cardiac outcomes among Fontan patients who have ever been pregnant versus those who have never been pregnant.

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Table 1. Patient and hospital characteristics of delivery hospitalizations with and without Fontan circulation, from 2000 to 2018 in the United States.

Characteristics	Non-Fontan deliveries		Fontan deliveries		SMD
	N	(%)	N	(%)	
Maternal age \geq 35 years	11,010,759	(15)	39	(8)	0.232
Maternal race/ethnicity					0.256
Black	8,397,822	(11)	50	(10)	
Hispanic	13,821,943	(19)	94	(19)	
None of the above	6,592,028	(9)	50	(10)	
Unknown	12,141,209	(17)	49	(10)	
White	32,156,279	(44)	266	(52)	
Obese (body mass index \geq 30 kg/m ²)	3,007,937	(4)	59	(12)	0.281
Payer					0.386
Medicare	423,260	(1)	15	(3)	
Medicaid	30,176,069	(41)	253	(50)	
Private insurance	38,098,421	(52)	211	(41)	
Self-pay	2,239,554	(3)	0	(0)	
No charge	134,296	(0)	0	(0)	
Other	1,916,223	(3)	30	(6)	
Median income quartile by ZIP code					0.111
Quartile 1	17,362,284	(24)	134	(26)	
Quartile 2	17,684,372	(24)	138	(27)	
Quartile 3	17,801,404	(24)	115	(23)	

Quartile 4	19,107,994	(26)	112	(22)	
Hospital region					0.253
Northeast	11,868,383	(16)	40	(8)	
Midwest	15,561,924	(21)	109	(21)	
South	27,664,417	(38)	221	(43)	
West	18,014,556	(25)	139	(27)	
Hospital teaching status					0.998
Rural	8,151,172	(11)	20	(4)	
Urban non-teaching	27,473,584	(38)	23	(5)	
Urban teaching	37,257,098	(51)	461	(91)	

SMD standardized mean difference.

Figure 1. Proportion of 2000-2018 delivery hospitalizations with Fontan circulation, in the United States.

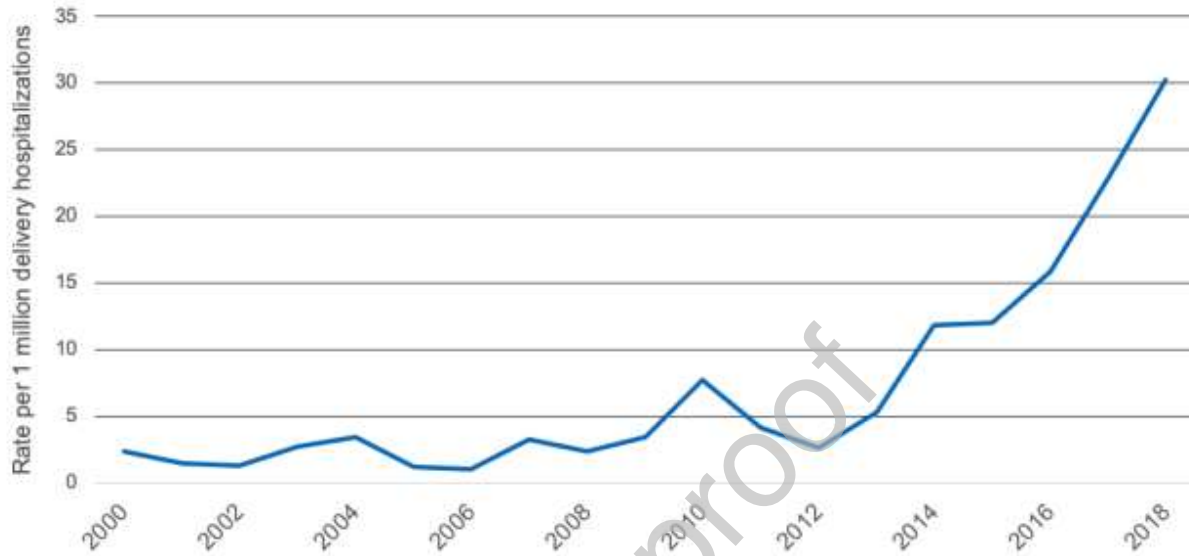
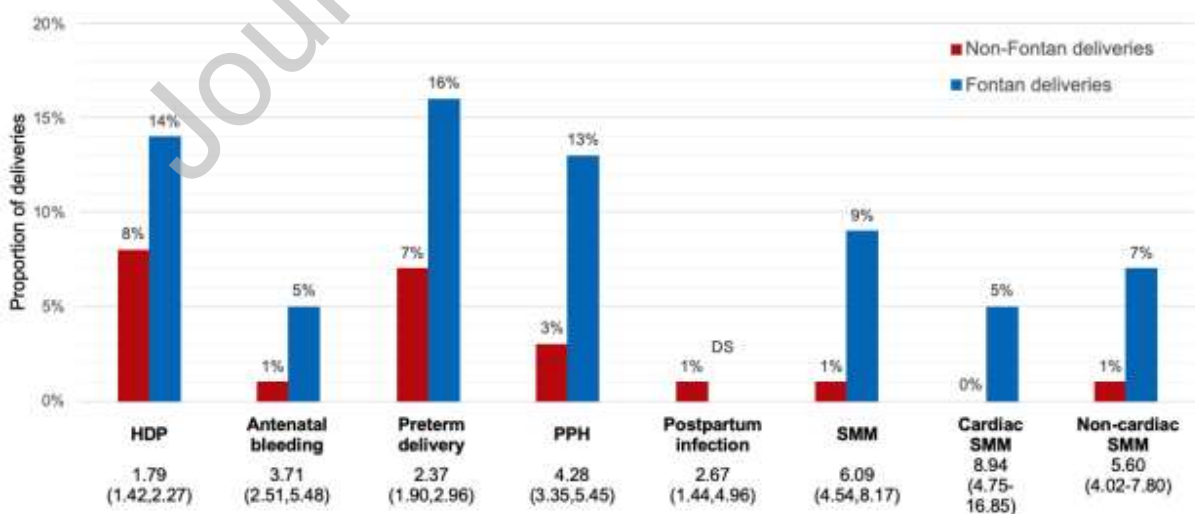


Figure 2. Obstetric complications of 2000-2018 delivery hospitalizations with and without Fontan circulation, in the United States.

Data represented as RR (95% CI), with non-Fontan deliveries as the reference group.

DS data suppressed (due to cell size); *HDP* hypertensive disorders of pregnancy; *PPH*

postpartum hemorrhage; *SMM* severe maternal morbidity



Supplemental Digital Content

Appendix 1. International Classification of Diseases-9-Clinical Modification (ICD-9-CM) and ICD-10-CM codes used in analysis.

Appendix 2. Obstetric outcomes of delivery hospitalizations with and without Fontan circulation, from 2000 to 2018 in the United States.

Journal Pre-proof