Outcomes of Pregnancy in Patients With Prior Right Ventricular Outflow Interventions

Alexander C. Egbe, MD, MPH; Majd El-Harasis, MD; William R. Miranda, MD; Naser M. Ammash, MD; Carl H. Rose, MD; Ayotola Fatola, BSc; Srikanth Kothapalli, MD; Mohamed Farouk Abdelsamid, MD; Heidi M. Connolly, MD

Background—The purpose of this study was to compare the incidence of pregnancy-related adverse outcomes (PRAO) between patients with versus without hemodynamically significant right ventricle outflow tract (RVOT).

Methods and Results—This was a retrospective cohort study of all pregnant patients with isolated RVOT lesions undergoing evaluation at the Mayo Clinic, 1990 to 2017. Hemodynamic significance was defined as ≥moderate pulmonary/conduit stenosis (≥3 m/s) and/or ≥moderate regurgitation. Patients with concomitant significant left heart disease were excluded. PRAO was defined as cardiovascular, obstetric, and/or neonatal complications occurring during the pregnancy through 6 weeks postpartum. A total of 224 pregnancies in 114 patients with RVOT lesions were identified; 38 pregnancies occurred in 24 patients with hemodynamically significant RVOT. Forty-eight (21%) pregnancies ended in spontaneous abortion. Of the 173 completed pregnancies, median gestational age at delivery was 38 (35–40) weeks and median birth weight 2965 (2065–4122) g. Seven pregnancies (4%) were complicated by cardiovascular events, 14 (8%) by obstetric complications, with adverse neonatal outcomes occurring in 38 (22%). There were no maternal deaths. The incidence of spontaneous abortion and PRAO were similar in both the RVOT and hemodynamically significant RVOT groups. As an isolated condition, Tetralogy of Fallot–pulmonary atresia was associated with spontaneous abortion and neonatal complications.

Conclusions—The risk of cardiovascular complications was low in patients with isolated RVOT lesions, and hemodynamically significant RVOT lesions were not associated with either cardiovascular complications or PRAO. Further studies are required to explore the factors responsible for PRAO in patients with Tetralogy of Fallot–pulmonary atresia. (J Am Heart Assoc. 2019;8: e011730. DOI: 10.1161/JAHA.118.011730.)

Key Words: cardiovascular complications • obstetric complications • pregnancy • prematurity

Because of continuing improvements in medical, transcatheter, and surgical therapies over the past several decades, the adult congenital heart disease (ACHD) population has grown significantly.1,2 More than 85% of children with congenital heart disease undergoing surgical or transcatheter interventions in the current era will survive into adulthood, with future pregnancy anticipated in some of the female patients.1–4 The complex antepartum, intrapartum, and postpartum hemodynamic changes may result in life-threatening complications in women with structural heart disease.4,5

Preconceptual counseling, risk stratification, and prompt identification and treatment of complications during pregnancy are important strategies to prevent, or at least potentially reduce adverse outcomes.4–8 Right ventricular outflow tract (RVOT) obstructive lesions account for more than two thirds of complex congenital heart disease diagnoses among newborns,9,10 and interventions for residual or recurrent RVOT lesions account for >20% of the procedures performed in ACHD patients.11 A common clinical dilemma encountered in counseling patients with isolated residual or recurrent RVOT lesions is to determine whether interventional therapy should be recommended before conception. Although several studies have proposed risk models for pregnancy-related adverse outcomes (PRAO) in ACHD patients with RVOT lesions, the majority of these models are confounded, to a great extent, by the presence of concurrent left heart obstruction, systemic ventricular dysfunction, mechanical prosthetic, and cyanosis.3,12–14 Consequently, at present only limited data exist regarding the risk of PRAO in women with isolated RVOT lesions,15 and such data will be important in deciding
whether interventional therapy should be recommended before proceeding with pregnancy.

The current study was designed to address 2 key questions: (1) What is the incidence of PRAO in patients with isolated RVOT lesions? and (2) Does the presence of a hemodynamically significant RVOT lesion (RVOT-HS) increase the risk of PRAO in this population?

Methods

Patient Selection

We will make data, analytic methods, and study materials available to other researchers upon request. We reviewed the Mayo Adult Congenital Heart Disease (MACHD) database and identified all women of childbearing age (age 18–50 years) with prior surgical and/or transcatheter RVOT interventions who received care during pregnancy at Mayo Clinic from January 1, 1990 through December 31, 2017. The Mayo Clinic institutional review board approved this study and waived informed consent for patients who provided research authorization. RVOT intervention was defined as surgical pulmonary valvotomy/valvectomy, transannular patch repair, surgical pulmonary valve replacement or right ventricular to pulmonary artery conduit placement, balloon pulmonary valvuoplasty, and transcatheter pulmonary valve replacement. We excluded women with significant left heart disease defined as prior mitral and/or aortic valve replacement, and significant (≥moderate) mitral, aortic, or subaortic lesions. We also excluded patients without delivery or postnatal follow-up data.

Data Collection

The last transthoracic echocardiogram performed within 12 months preceding conception or the first echocardiogram performed in the first trimester (when preconception echocardiogram was not available) was considered the baseline echocardiogram. Images were reviewed and hemodynamic variables collected from the baseline echocardiogram, last echocardiogram before delivery, and last echocardiogram within the study period. The severity of tricuspid regurgitation, pulmonary/conduit regurgitation, RV enlargement, and RV systolic dysfunction were graded as none/trivial, mild, mild–moderate, moderate, moderate–severe, and severe based on standard assessment by comprehensive echocardiogram.\textsuperscript{16,17} Obstetric records and discharge summaries were reviewed to determine the occurrence of PRAO.

End Points and Definitions

The primary objective was to determine the incidence of PRAO outcomes in patients with prior RVOT interventions, and compare this risk with historic data of pregnancy outcomes in adults with congenital heart disease.\textsuperscript{3,12–14} The secondary objective was to assess the impact of RVOT-HS lesions on PRAO in this study cohort. In order to assess the relationship between RVOT-HS lesions and PRAO, we defined hemodynamically significant RVOT lesions as moderate pulmonary/conduit stenosis (peak continuous wave Doppler velocity ≥3 m/s) and/or ≥moderate regurgitation based on hemodynamic variables from the baseline echocardiogram.

PRAO was defined as a composite of cardiovascular, obstetric, and neonatal complications. In concordance with previous studies,\textsuperscript{3,12–14} cardiovascular complications were defined as heart failure (pulmonary edema or peripheral edema requiring oral or intravenous diuretics), sustained atrial or ventricular arrhythmias, ischemic or hemorrhagic stroke, urgent invasive cardiac procedures during pregnancy or within 6 months after delivery, and cardiovascular death. Obstetric complications were defined as gestational hypertension (new onset of systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg), pre-eclampsia (gestational hypertension with ≥300 mg/L proteinuria per 24-hour sample), eclampsia (hypertension-related seizures), hemolysis-elevated liver enzymes–low platelets syndrome, postpartum hemorrhage (blood loss >500 mL during vaginal delivery or >1000 mL during cesarean section within 24 hours of delivery, which required transfusion or was accompanied by a drop in hemoglobin >2 g/L), and noncardiac death during delivery. Neonatal complications were defined as premature birth (<37 weeks gestation), small-for-gestational-age birth weight (<10th percentile), respiratory distress syndrome, intraventricular hemorrhage, fetal death (>20 weeks gestation), or neonatal death (within 28 days after birth). For purposes of analysis, if a patient experienced ≥1 complication in the same category, this was recorded as a single event. All pregnancy losses before 20 weeks gestation were classified
as spontaneous abortion, while continuation of pregnancy beyond 20 weeks was considered completed pregnancy.

Statistical Analysis
Data were presented as mean±SD, median (interquartile range), or counts (%), and between-group comparisons were performed using $\chi^2$ test and Fisher exact test as appropriate. The association between patient-specific risk factors including severity of RVOT lesion and the occurrence of PRAO was assessed using a univariable Cox proportional hazards model, and expressed as hazard ratio and 95% CI. For the estimation of incidence of PRAO and the risk factors for PRAO, each pregnancy was considered a separate event. All statistical analyses were performed with JMP software (version 13.0; SAS Institute Inc, Cary, NC), and a $P<0.05$ was considered statistically significant.

Results
Baseline Clinical and Echocardiographic Data
Out of 502 female patients of childbearing age with a history of RVOT interventions, 114 patients met the study inclusion criteria (Figure 1). The clinical and echocardiographic data at the time of initial evaluation are shown in Table 1. The 2 most common structural diagnoses were tetralogy of Fallot (TOF) with subpulmonic stenosis followed by valvular pulmonic stenosis. Only 16 (14%) patients had their native pulmonary valve at the time of pregnancy. The median gravidity was 1 (range: 1–7). Four of the patients required a vitamin K antagonist for paroxysmal atrial arrhythmias before conception, but none of the patients were treated with anticoagulation during pregnancy. The average number of echocardiograms performed during pregnancy was 2±1 per patient. A total of 91 (80%) patients had echocardiograms in the first trimester at mean gestational age of 9±2 weeks, 112 (98%) patients had echocardiograms in the second trimester at mean gestational age of 21±3 weeks, and 86 (75%) patients had echocardiograms in the third trimester at mean gestational age of 33±2 weeks.

Pregnancy and Delivery Data
The 114 patients had a total of 224 pregnancies, of which 2 (0.9%) were conceived with intrauterine insemination, and 1 (0.4%) via in vitro fertilization. There were 48 (21%) cases of first trimester spontaneous abortion and 3 (1%) terminations of pregnancy.

Indications for terminations included fetal hypoplastic left heart syndrome identified at 21 weeks gestation, and heart failure with sustained ventricular tachycardia in the setting of severe tricuspid and pulmonary regurgitation at 13 weeks gestation. The third case of termination of pregnancy was for tubal pregnancy at 9 weeks gestation and tubal ligation was performed during the same procedure. The incidence of spontaneous abortion was significantly different between the disease groups: TOF–pulmonic stenosis (20/106, 19%) versus TOF–pulmonary atresia (15/36, 42%) versus pulmonary atresia with intact ventricular septum (5/20, 25%) and valvular pulmonic stenosis (8/61, 13%), $P=0.008$.

A total of 173 completed pregnancies (Table 2) were included in the analysis. The median gestational age at the time of delivery was 38 (35–40) weeks and median birth weight was 2965 (2065–4122) g. Apgar score was available in 116 (67%) babies and mean score was 8±1. There was 1 twin gestation, and 86 (49%) of the 174 babies were male. Delivery was by cesarean section in 26 (15%) cases; the indications were fetal distress ($n=7$), arrest/failure of progression of labor ($n=7$), fetal malpresentation ($n=2$), repeat (elective) cesarean section ($n=6$), and multiple indications ($n=4$).

Pregnancy-Related Adverse Outcomes
Table 2 shows the different cardiovascular and obstetric neonatal complications during pregnancy. The cardiovascular complications observed were heart failure and arrhythmias, and these were managed conservatively without need for hospitalization or interventions. The total counts of complications observed were 10 (4%) cardiovascular, 16 (6%) obstetric, and 75 (22%) neonatal complications (Figure 2). There were 3 neonates with congenital heart disease, of which 2 had TOF–pulmonary atresia and 1 coarctation of the aorta with large ventricular septal defect. In all 3 cases the maternal diagnosis was TOF–pulmonic stenosis; none of the mothers had genetic diagnosis of 22q11 deletion. One infant was diagnosed with trisomy 21 (Down syndrome) without

Figure 1. Flowchart showing cohort selection. h/o indicates history of; LH, left heart; RVOT, right ventricle outflow tract.
congenital heart disease, and the maternal age was 42 years. The only neonatal death occurred in the infant who had coarctation of aorta and large ventricular septal defect and who also had multiple extracardiac congenital malformations.

### Hemodynamically Significant RVOT Lesions

Of the 173 pregnancies, 38 (22%) pregnancies in 24 patients occurred in the setting of RVOT-HS lesions as follows: severe pulmonary regurgitation (n=8, 5%), mixed moderate/severe stenosis and regurgitation (n=24, 14%), and ≥moderate pulmonary valve/conduit stenosis (n=6, 4%). Compared with the remainder of the cohort, the pregnancies that occurred in the setting of RVOT-HS lesions experienced a similar incidence of spontaneous abortions and other PRAO (Figure 3). However, as an individual entity, TOF–pulmonary atresia was associated with increased rates of both spontaneous abortion (hazard ratio 2.79, 95% CI 2.33–3.17, P=0.001) and neonatal complications (hazard ratio 1.84, 95% CI 1.09–2.37, P=0.024), Table 3. Of the 28 pregnancies that occurred in the 26 patients with TOF–pulmonary atresia, 9 occurred in the setting of RVOT-HS. In the subsets of patient with TOF–pulmonary atresia, there was no significant difference in the incidence of PRAO between those with RVOT-HS versus those without RVOT-HS (cardiac complications 5.1% versus 5.9%, P=0.616; obstetric complications 9.3% versus 9.5%, P=0.814; and neonatal complications 29% versus 28%, P=0.711).

An exploratory analysis was performed to determine whether severe valve/conduit stenosis defined as peak velocity >4 m/s was associated with PRAO. There are only 2 patients with peak velocity >4 m/s, thereby precluding any meaningful statistical analysis. We also performed exploratory analysis...
analysis to determine whether preoperative cardiac magnetic resonance imaging–derived volumetric indices were associated with PRAO. Of the 32 patients with ≥moderate pulmonary regurgitation, cardiac magnetic resonance imaging–derived volumetric indices were available in 21 patients. Using the median right ventricular end-diastolic volume, end-systolic volume, and ejection fraction as cut-off points, there was no association between cardiac magnetic resonance imaging–derived volumetric indices and occurrence of PRAO.

The mean follow-up from first pregnancy to end of study interval was 4.3±1.4 years for the 24 patients with RVOT-HS lesions. During this period, 7 of the 24 patients underwent pulmonary valve replacement; the other 17 patients did not experience any symptomatic deterioration, progression of RVOT lesion, or deterioration of RV function.

### Discussion

In this study of 114 patients with RVOT lesions, the incidence of cardiovascular complications during pregnancy was 4%, regardless of the presence or absence of RVOT-HS lesions. Previous work has described the incidence and risk factors for cardiovascular complications during pregnancy in patients with structural heart disease to be 8% to 20%. Previous predictive factors are remarkably consistent, implicating systemic ventricular dysfunction, left heart obstruction, mechanical prosthesis, and cyanosis in cardiovascular complications. Patients with RVOT lesions are not generally considered to be at high risk for cardiovascular events during pregnancy even though there are very limited data of outcomes in this population to support or refute this notion.

In a recent study of pregnancy outcomes in women with allograft RVOT conduits, Romeo et al reported a 6% incidence of cardiovascular complications (no deaths), but subgroup analysis of differential risk based on the severity of residual RVOT lesion (a modifiable risk factor) was not performed, perhaps because of small sample size. In addition to reporting a similar frequency of cardiovascular complications, the current study also demonstrates that the risk of cardiovascular complications remains low even in the setting of a hemodynamically significant residual RVOT lesion at the time of conception. This has profound implications for counseling on the merits of preconceptual interventional therapy for an asymptomatic patient with a RVOT-HS lesion in anticipation of the further hemodynamic stress of pregnancy. Among the 24 patients with RVOT-HS lesions, 11 patients went on to have multiple pregnancies (without cardiac interventions between pregnancies) without cardiovascular complications. There was no symptomatic or hemodynamically significant deterioration in the patients who did not undergo interventions during follow-up. These findings, despite the limitations of a retrospective study, suggest that the timing of surgical or transcatheter interventions should not be influenced by future reproductive intent.

We also observed spontaneous abortions in 21% of the pregnancies in this cohort. A subgroup analysis showed that the incidence of spontaneous abortion varied by underlying

### Table 2. Pregnancy Data for Completed Pregnancies

|                      | n=173 |
|----------------------|-------|
| Maternal age, y      | 29±5  |
| Vaginal delivery     | 147 (85%) |
| Spontaneous          | 91    |
| Induced              | 58    |
| Assisted second stage| 42 (29%) |
| Forceps              | 41    |
| Vacuum               | 1     |
| Cesarean section     | 26 (15%) |
| CHD diagnosis*       |       |
| TOF with pulmonic stenosis | 84 (49%) |
| TOF with pulmonary atresia | 21 (12%) |
| Pulmonary atresia with IVS | 15 (9%) |
| Valvular pulmonic stenosis | 53 (31%) |
| Cardiovascular complications* |       |
| Heart failure        | 5 (3%) |
| Sustained atrial arrhythmia | 4 (2%) |
| Sustained ventricular arrhythmia | 1 (0.6%) |
| Stroke               | 0     |
| Urgent cardiovascular intervention | 0  |
| Cardiovascular death | 0     |
| Obstetric complications* |       |
| Pregnancy-induced hypertension | 4 (2%) |
| Pre-eclampsia        | 6 (4%) |
| Eclampsia            | 0     |
| HELLP syndrome       | 1 (0.6) |
| Postpartum hemorrhage| 5 (3%) |
| Noncardiac death     | 0     |
| Neonatal complications* |       |
| Prematurity           | 26 (15%) |
| Small-for-gestational-age birth weight | 31 (18%) |
| Respiratory distress syndrome | 12 (7%) |
| Intraventricular hemorrhage | 2 (1%) |
| Fetal death          | 0     |
| Neonatal death       | 1 (0.6%) |

Although 1 of the terminations of pregnancy occurred at 21 weeks, that particular pregnancy was not counted as a completed pregnancy. CHD indicates congenital heart disease; HELLP, hemolysis, elevated liver enzyme, low platelet; IVS, intact ventricular septum; TOF, tetralogy of Fallot.

*All calculations based on total number of completed pregnancies (n=173).
diagnosis, ranging from 13% in patients with valvular pulmonic stenosis to as high as 42% in patients with TOF–pulmonary atresia. Other studies have reported spontaneous abortion in 3% to 19% of pregnancies in patients with congenital heart disease, and genetic and hemodynamic factors have been proposed as potential causes of spontaneous abortion in these patients.12–14,18 Patients with TOF–pulmonary atresia are known to have high prevalence of genetic abnormalities including 22q11 deletion, and several studies have shown increased risk of first trimester spontaneous abortions in patients with genetic and chromosomal abnormalities.20–22 We speculated that genetic factors may be responsible for the particularly high occurrence of spontaneous abortions in patients with TOF–pulmonary atresia, although we cannot confirm this speculation because most of the patients did not have testing. Although hemodynamic factors have been postulated as a potential cause of spontaneous abortion in this population, we did not observe any association between abortion and severity of RVOT lesions in our cohort. We do not think that hemodynamic factors contribute significantly to spontaneous abortion because the peak hemodynamic stress of pregnancy occurs in the second and third trimesters, which is much later than the timing of spontaneous abortions that is usually in the first trimester.

We also observed neonatal complications in 22% of pregnancies, mostly because of prematurity and small-for-gestational age. TOF–pulmonary atresia diagnosis was associated with an increased risk of neonatal complications. A recent study of pregnancy outcomes in women with allograft RVOT conduits identified severe pulmonary regurgitation as a risk factor for neonatal complications, in particular preterm delivery.15 In contrast, we did not observe any difference in the incidence of neonatal events based on the severity of the maternal RVOT lesion. A possible explanation for the discordant findings might lie in the population demographics: We studied patients with isolated RVOT lesions while

Figure 2. Bar graphs showing the incidence of spontaneous abortion and pregnancy-related adverse outcomes. Data from the current study shown in blue (Egbe et al) are compared side by side to ZAHARA study12; Drenthen et al2; CARPREG study13; and Khairy et al.14 *Data about obstetric complication were unavailable in the Drenthen et al study.
excluding those with significant left heart disease, while 30% of their patients in the Romeo et al study had primary aortic valve disease and received RVOT allograft conduits as a component of the Ross operation; only 4 patients with TOF–pulmonary atresia were included. Some authors have proposed abnormal maternal hemodynamics with resultant placental insufﬁciency as the pathophysiologic mechanism for prematurity and small-for-gestational-age deliveries in patients with congenital heart disease.\(^4\,\!^{13,23}\) Patients with TOF–pulmonary atresia have abnormal pulmonary arterial architecture and often require multiple arterioplasties with prosthetic materials.\(^24\) It would seem reasonable to hypothesize abnormal pulmonary vascular function leading to suboptimal response to the obligatory increase in pulmonary blood flow during gestation, potentially resulting in placental insufﬁciency.

**Table 3.** Univariable Risk Factors for Pregnancy-Related Adverse Outcomes

|                        | Abortions     | Cardiovascular | Obstetric        | Neonatal     |
|------------------------|---------------|----------------|------------------|--------------|
|                        | HR (95% CI)   | HR (95% CI)    | HR (95% CI)      | HR (95% CI)  |
| Age >35 y              | 2.14 (0.75–6.11) | 1.84 (0.43–2.33) | 1.98 (0.86–2.75) | 1.54 (0.84–3.11) |
| TOF with pulmonic stenosis | 1.43 (0.84–2.96) | 1.02 (0.63–1.98) | 1.07 (0.71–2.89) | 0.97 (0.49–1.95) |
| TOF with pulmonary atresia | 2.79 (2.33–3.17) | 2.07 (0.65–5.32) | 1.87 (0.78–3.94) | 1.84 (1.09–3.27) |
| Pulmonary atresia with IVS | 1.86 (0.54–3.94) | 1.65 (0.87–2.68) | 0.85 (0.11–4.19) | 1.01 (0.44–3.82) |
| Valvular pulmonic stenosis | 0.80 (0.46–0.97) | 0.91 (0.66–1.06) | 1.03 (0.67–1.98) | 0.88 (0.62–1.02) |
| Native pulmonary valve | 0.88 (0.35–1.04) | 1.04 (0.42–3.76) | 1.08 (0.67–2.74) | 0.85 (0.33–1.97) |
| Hemodynamically significant RVOT lesion* | 1.47 (0.96–2.62) | 1.21 (0.27–4.11) | 1.06 (0.72–3.54) | 1.65 (0.14–2.83) |
| LV ejection fraction <40% | 1.06 (0.74–1.92) | 1.54 (0.43–2.99) | 1.12 (0.57–2.87) | 1.44 (0.87–3.66) |
| ≥Moderate RV systolic dysfunction | 1.75 (0.21–4.18) | 1.76 (0.92–3.93) | 1.18 (0.49–2.78) | 1.94 (0.81–3.47) |
| ≥Moderate tricuspid regurgitation | 2.63 (0.55–6.13) | 2.16 (0.98–3.87) | 1.09 (0.28–4.11) | 1.63 (0.71–4.16) |

HR indicates hazard ratio; IVS, intact ventricular septum; LV, left ventricle; RV, right ventricle; RVOT, right ventricle outﬂow tract; TOF, tetralogy of Fallot.

*Defined as moderate pulmonary/conduit stenosis (≥3 m/s) and/or ≥ moderate regurgitation based on hemodynamic variables from the baseline echocardiogram.
Limitations
This is a retrospective single center study and is therefore prone to referral bias. The study population was relatively small, which limited our ability to perform multivariable analysis. In contrast to previous studies of pregnancy outcomes in congenital heart disease that enrolled patients with a wide spectrum of diagnoses, the current study focuses exclusively on a homogeneous subset of patients with isolated RVOT lesions, and this homogeneity increases the internal validity of our results. Another limitation was that we defined the hemodynamic significance of residual RVOT lesions based on quantitative and qualitative echocardiographic assessment without integrating invasive hemodynamic and cross-sectional imaging data.

Conclusions
In this study of patients with isolated RVOT lesions during pregnancy, we showed that the risk of cardiovascular complications was low, and that the severity of residual RVOT lesion was not associated with PRAO. Some of the patients with RVOT-HS lesions who did not undergo surgical interventions tolerated subsequent pregnancies without either symptomatic or hemodynamic deterioration. Patients with TOF–pulmonary atresia appear to be at significantly higher risk for spontaneous abortions and neonatal complications. Further studies are required to explore the factors responsible for PRAO in patients with TOF–pulmonary atresia. Given that so many of the ACHD patients have isolated RVOT lesions, we hope that this study serves as a “pilot” for a larger, multicenter investigation.

Even within the context of the limitations of a retrospective study, our results suggest that the timing of surgical or transcatheter interventions should not be influenced by the anticipated effects of future pregnancy in these patients. These data are important for evidenced-based counseling and clinical decision making in this subset of ACHD patients.

Sources of Funding
Dr Egbe is supported by National Heart, Lung, and Blood Institute (NHLBI) grant K23 HL141448-01.

Disclosures
None.

References
1. Gibboa SM, Devine OJ, Kucik JE, Oster ME, Riehle-Colarusso T, Nembhard WN, Xu P, Correa A, Jenkins K, Marelli AJ. Congenital heart defects in the United States: estimating the magnitude of the affected population in 2010. Circulation. 2016;134:101–109.
2. Marelli AJ, Themistocli J, Mackie AS, Ionescu-Ittu R, Pilote L. Planning the specialized care of adult congenital heart disease patients: from numbers to guidelines; an epidemiologic approach. Am Heart J. 2009;157:1–8.
3. Drenthen W, Pieper PG, Roos-Hesselink JW, van Lottum WA, Voors AA, Mulder BJ, van Dijk AP, Vliegen HW, Yap SC, Moons P, Ebels T, van Veldenheuvel DJ, ZAHARA Investigators. Outcome of pregnancy in women with congenital heart disease: a literature review. J Am Coll Cardiol. 2007;49:2303–2311.
4. Elkayam U, Goland S, Pieper PG, Silversides CK. High-risk cardiac disease in pregnancy: part II. J Am Coll Cardiol. 2016;68:502–516.
5. Warnes CA. Pregnancy and delivery in women with congenital heart disease. Circ J. 2015;79:1416–1421.
6. Stout KK, Daniels CJ, Aboulhosn JA, Bozkurt B, Broberg CS, Colman JM, Crumb SR, Dearani JA, Fuller S, Gurvitz M, Khairy P, Landzberg MJ, Saidi A, Valente AM, Van Hare GF. 2018 AHA/ACC guideline for the management of adults with congenital heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2018;72(12):e81–e192.
7. Baumgartner H, Bonhoeffer P, De Groot NM, De Haan F, Deanfield JE, Galie N, Gatzoulis MA, Gohlke-Beerswolf C, Kaeurnerer H, Kilner P, Meijboom F, Mulder BJ, Oechslin E, Oliver JM, Serraf A, Szatmari A, Thaulow E, Vouhe PR, Walma J, Task Force on the Management of Grown-up Congenital Heart Disease of the European Society of Cardiology (ESC); Association for European Paediatric Cardiology (AEPCC); ESC Committee for Practice Guidelines (CPG). ESC Guidelines for the management of grown-up congenital heart disease (new version 2010). Eur Heart J. 2010;31:2915–2957.
8. Silversides CK, Kress M, Beauchesne L, Bradley T, Connelly M, Niwa K, Mulder B, Webb G, Colman J, Therrien J. Canadian Cardiovascular Society 2009 Consensus Conference on the management of adults with congenital heart disease: outcome tract obstruction, coarctation of the aorta, tetralogy of Fallot, Ebstein anomaly and Marfan’s syndrome. Can J Cardiol. 2010;26:e80–e97.
9. Egbe A, Uppu S, Stroustrup A, Lee S, Ho D, Srivastava S. Incidences and sociodemographics of specific congenital heart diseases in the United States of America: an evaluation of hospital discharge diagnoses. Pediatr Cardiol. 2014;35:975–982.
10. Egbe A, Uppu S, Lee S, Ho D, Srivastava S. Changing prevalence of severe congenital heart disease: a population-based study. Pediatr Cardiol. 2014;35:1232–1238.
11. Mascio CE, Pasquali SK, Jacobs JP, Jacobs ML, Austin EH III. Outcomes in adult congenital heart surgery: analysis of the Society of Thoracic Surgeons database. J Thorac Cardiovasc Surg. 2011;142:1090–1097.
12. Drenthen W, Boersma E, Balci A, Moons P, Roos-Hesselink JW, Mulder BJ, Vliegen HW, van Dijk AP, Voors AA, Yap SC, van Veldenheuvel DJ, Pieper PG, ZAHARA Investigators. Predictors of pregnancy complications in women with congenital heart disease. Eur Heart J. 2010;31:2124–2132.
13. Su SC, Sermer M, Colman JM, Alvarez AN, Mercier LA, Morton BC, Kells CM, Bergin ML, Kiess MC, Marcotte F, Taylor DA, Gordon EP, Spears JG, Terris NM, Amankwah KS, Smallhorn JF, Farine D, Sorensen S; Cardiac Disease in Pregnancy (CAPPREG) Investigators. Prospective multicenter study of pregnancy outcomes in women with heart disease. Circulation. 2001;104:515–521.
14. Khairy P, Ouyang DW, Fernandes SM, Lee-Parrtiz A, Economy KE, Landzberg MJ. Pregnancy outcomes in women with congenital heart disease. Circulation. 2006;113:517–524.
15. Romeo JL, Takkenberg JM, Roos-Hesselink JW, Hanf M, Cornette JMJ, van Leeuwen WJ, van Dijk A, Bogers A, Mokhles MM. Outcomes of pregnancy after right ventricular outflow tract reconstruction with an allograft conduit. J Am Coll Cardiol. 2018;71:2656–2665.
16. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W, Voigt JD. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2015;28:1–39.e14.
17. Zoghbi WA, Adams D, Bonow RO, Enriquez-Sarano M, Foster E, Grayburn PA, Hahn RT, Han Y, Hung J, Lang RM, Little SH, Shah DJ, Seshan S, Thavendiranathan P, Thomas JD, Weissman NJ. Recommendations for noninvasive evaluation of native valvular regurgitation: a report from the American Society of Echocardiography developed in collaboration with the society for cardiovascular magnetic resonance. J Am Soc Echocardiogr. 2017;30:303–371.
18. Thorne S, MacGregor A, Nelson-Piercy C. Risks of contraception and pregnancy in women with heart disease. Heart. 2006;92:1520–1525.
19. Balci A, Sollie-Szarynska KM, van der Bijl AG, Ruys TP, Mulder BJ, Roos-Hesselink JW, van Dijk AP, Wajon EM, Drenthen W, Hilleges HL, Aarnoudse JG, van Veldhuisen DJ, Pieper PG; ZAHARA-II investigators. Prospective validation and assessment of cardiovascular and offspring risk models for pregnant women with congenital heart disease. *Heart*. 2014;100:1373–1381.

20. Fung WL, Chow EW, Webb GD, Gatzoulis MA, Bassett AS. Extracardiac features predicting 22q11.2 deletion syndrome in adult congenital heart disease. *Int J Cardiol*. 2008;131:51–58.

21. Swaby JA, Silversides CK, Bekeschus SC, Piran S, Oechslin EN, Chow EW, Bassett AS. Complex congenital heart disease in unaffected relatives of adults with 22q11.2 deletion syndrome. *Am J Cardiol*. 2011;107:466–471.

22. Boue J, Boue A. Genetic counselling and prenatal diagnosis for chromosome anomalies. Use of study of spontaneous abortions. *Int J Gynaecol Obstet*. 1976;14:290–295.

23. Pundi KN, Pundi K, Johnson JN, Dearani JA, Bonnichsen CR, Phillips SD, Canobbio MC, Driscoll DJ, Cetta F. Contraception practices and pregnancy outcome in patients after Fontan operation. *Congenital Heart Dis*. 2016;11:63–70.

24. Reddy VM, McElhinney DB, Amin Z, Moore P, Parry AJ, Teitel DF, Hanley FL. Early and intermediate outcomes after repair of pulmonary atresia with ventricular septal defect and major aortopulmonary collateral arteries: experience with 85 patients. *Circulation*. 2000;101:1826–1832.

DOI: 10.1161/JAHA.118.011730