International Fetal Cardiac Intervention Registry

A Worldwide Collaborative Description and Preliminary Outcomes

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ABSTRACT

BACKGROUND Invasive fetal cardiac intervention (FCI) has been reported in single-institution series, promoting technical and physiologic success.

OBJECTIVES This study describes the creation of an international registry of cases presenting for FCI, intended to compile technical and outcome data from a multicenter cohort.

METHODS For this initial analysis, the entire database of the International Fetal Cardiac Intervention Registry (IFCIR) was queried for details of diagnoses, procedures, and outcomes. Maternal-fetal dyads from January 2001 through June 2014 were included.

RESULTS Eighteen institutions submitted data by data harvest. Of 370 cases entered, 245 underwent FCI: 100 aortic valvuloplasties from a previous single-center report (excluded from additional reporting here), an additional 86 aortic and 16 pulmonary valvuloplasties, 37 atrial septal cases, and 6 unclassified cases. FCI did not appear to affect overall survival to hospital discharge. Among live-born infants with a fetal diagnosis of aortic stenosis/evolving hypoplastic left heart syndrome, more than twice as many were discharged with biventricular circulation after successful FCI versus those meeting institutional criteria but without any or successful FCI (42.8% vs. 19.4%, respectively). When fetal deaths were counted as treatment failures, the percentages were similar: biventricular circulation at discharge was 31.3% versus 18.5% for those discharged with univentricular palliation. Survival to discharge for live-born fetuses with atrial restriction was similar to that of those undergoing technically successful versus unsuccessful FCI (63.6% vs. 46.7%, respectively), although criteria for diagnosis were nonuniform.

CONCLUSIONS We describe the contents of the IFCIR and present post-natal data to suggest potential benefit to fetal therapy among pregnancies considered for possible intervention and support proposals for additional work. (J Am Coll Cardiol 2015;66:388–99) © 2015 by the American College of Cardiology Foundation.

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C ongenital heart disease, which occurs in approximately 6 of 1,000 live births (1), is the most common cause of infant death due to birth defect in the United States and other developed countries. The development of maternal-fetal surgery techniques and advances in ultrasonography technology have permitted treatment of some congenital defects during fetal life (2,3). From a historical perspective particular to cardiac intervention, in 1991 Maxwell et al. (4) published their first technically successful attempts to dilate the stenotic aortic valve in 2 mid trimester fetuses, using balloon valvuloplasty via a needle inserted in the left ventricle, aiming to prevent development of left heart hypoplasia. In 2004, a team from Boston showed feasibility and moderate success in a series of fetal balloon valvuloplasties for severe aortic stenosis (AS) (5). Other fetal cardiac interventions were subsequently described using a similar approach, specifically, balloon pulmonary valvuloplasty for severe pulmonary stenosis and pulmonary atresia with an intact ventricular septum (PS+PA/IVS) (6,7), and atrial septoplasty or stent placement for an intact or highly restrictive atrial septum in fetuses with hypoplastic left heart syndrome (HLHS) (8).

Following this pioneering work, an increasing number of centers began offering fetal cardiac intervention (FCI), primarily for midgestation severe AS, which is thought, without intervention, to progress to HLHS by term (9). Given the rarity of suitable cases, prospective evaluation of outcomes with appropriate control groups may be extremely difficult. We therefore proposed initiation of an international registry of procedures performed to date, with options for both the retrospective and the prospective registration of candidates for fetal intervention (regardless of whether a procedure was performed). Our premise was that such a registry would allow for more rapid accumulation of combined experience with FCI than a single-center effort.

Thus, for this report, our main objective was to describe the development and introduction of a Research Electronic Data Capture (REDCap) database of pregnant women, their fetuses, and infants evaluated at various international programs as FCI candidates. Our secondary objectives were to describe the content of the new International Fetal Cardiac Intervention Registry (IFCIR) after enrollment of most of the eligible sites and completion of their case entries and to compile data to support proposals for additional publications and trials in this area.

METHODS

The present study is the initial report of data collected both retrospectively and prospectively in the IFCIR. It is a voluntary registry that collects pregnancy, perinatal, operative, and perioperative data for patients (maternal/fetal dyads and newborn infants) whom specialists believed would benefit from intervention based on fetal echocardiographic criteria, including those who eventually were not candidates because of other fetal noncardiac conditions or maternal conditions or preferences.

Collected data included basic demographic information, descriptive anatomic diagnoses, associated noncardiac or genetic anomalies, IFCIR-defined fetal procedures, pre-operative factors, maternal/fetal intraoperative details, FCI and post-natal surgical procedures performed, complications incurred at the time of or after fetal intervention through the remainder of pregnancy, technical success of the FCI procedure (defined as balloon dilation of the intended target structure or stent placement with patency and stable position at the conclusion of the procedure), and in-hospital neonatal/infant mortality (through to first discharge). Diagnoses and procedures were entered by clinicians and affiliated data managers. A complete list of data collected is available in the Online Appendix. Procedures included perventricular fetal aortic valvuloplasty (FAV), perventricular fetal pulmonary valvuloplasty (FPV), and transatrial fetal atrial septoplasty and/or stent placement. Fetal pacemaker implantation and therapeutic hyperoxia were included in the database but were not included

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in the initial data harvest. For this initial report, data that had been entered as of June 2014 were queried.

DATABASE DESIGN AND DATA ENTRY PROTOCOL. Approximately 25 fetal surgery and fetal interventional programs worldwide initially committed to or expressed interest in contributing data to this effort (10). Beginning in 2011, a World Wide Web-based REDCap database was launched, designed by University of California-San Francisco (UCSF) site participants with content and structural input from the other collaborators over a 6-month period. Local data entry personnel were identified and assigned unique, secure sign-in credentials and received telephone or Web-based training. Data from all consecutive cases undergoing evaluation for FCI since 2001 were requested. During data entry, sites were granted access only to their own data by use of a "Data Access Group" function in REDCap. In rare cases involving referral of a patient across centers, data entry personnel were asked to communicate with each other and avoid duplicate entries. Patients sent from a nonintervention center to an intervention center were entered by the center performing the intervention only.

UCSF serves as the administrative and data-coordinating center for IFCIR and obtained institutional review board (IRB) approval for the project. Individuals and participating member sites (see complete list in Online Appendix) obtained local IRB and ethics board approval or a waiver, as governed by applicable local legal and research standards.

De-identified study data were entered remotely at the local institutions and collected and managed using REDCap electronic data capture tools hosted at UCSF (11). REDCap is a Web-based application designed to support data capture for research studies.

STATISTICAL ANALYSIS. Data analysis was performed at the UCSF administrative center site and at the data analysis center at Baylor College of Medicine, using SPSS Statistics version 22.0 software (IBM, Armonk, New York) for Windows (Microsoft, Redmond, Washington). Maternal, fetal, and neonatal outcomes were described using standard summary statistics and nonparametric testing as appropriate. Frequencies are reported along with percentages, and means with SD and medians with interquartile ranges are reported. Patients with missing data were excluded from analyses involving that variable but were included in the overall reporting as appropriate.

Additional analyses were considered exploratory and not subjected to statistical analysis; we performed simple evaluations, with important limitations (primarily lack of true case-control design), of overall outcomes for 2 diagnostic groups: fetuses with AS and fetuses with HLHS and a highly restrictive or intact atrial septum. Two tallies were performed for each diagnostic group. First, an intention-to-treat analysis that contrasted the outcomes of all fetuses in the FCI group versus a group meeting criteria but who did not undergo FCI (**Table 1**). In this instance, fetal periprocedural demise or late intrauterine demise was regarded as a failed outcome. Given the expected wide variation in center experience and different levels of skill associated with different technical success rates and procedure-related fetal mortality, a second tally for each diagnostic group was performed. In this second analysis, only those live-born infants with technically successful FCI were included and then contrasted with live-born infants who met criteria but who either did not have FCI or who had a technically unsuccessful FCI. This allowed an estimate of outcomes under ideal circumstances, with all FCI achieving technical success without any fetal deaths. The entire exploratory exercise was designed to provide a general overview of the range of outcomes among patients considered for intervention. Pregnancies resulting in elective termination were excluded from the analyses.

CRITERIA FOR ENTRY INTO EXPLORATORY ANALYSIS. The fetal AS group included fetuses who were deemed candidates for FAV by the participating

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TABLE 1 Suggested Preoperative Echocardiographic Criteria*† With Threshold Z Scores‡ for Performance of Balloon Valvuloplasty§

1. Dominant cardiac anatomic anomaly: valvular aortic stenosis with all of the following:
   - Decreased mobility of valve leaflets
   - Antegrade Doppler color flow jet across aortic valve smaller than valve annulus diameter
   - No or minimal subvalvular LV outflow obstruction

2. LV function qualitatively depressed

3. Either retrograde or bidirectional flow in the transverse aortic arch or 2 of the following:
   - Monophasic mitral inflow Doppler pattern
   - Left-to-right flow across atrial septum or intact atrial septum
   - Bidirectional flow in pulmonary veins

4. LV long-axis Z score ≥2

5. Threshold score >4 (fulfilling >4 of the following)
   - LV long-axis Z score >0 (1 point)
   - LV short-axis Z score >0 (1 point)
   - Aortic annulus Z score ≥3.5 (1 point)
   - Mitral valve annulus Z score of ≥2 (1 point)
   - Mitral regurgitation or aortic outflow peak systolic gradient >20 mm Hg (1 point)

*Criteria are presented in table form for completeness. Registry retrospective analysis considered only decreased left ventricular function, retrograde aortic arch Doppler flow, and left-to-right atrial shunting as necessary and a decision to intervene as sufficient. †All criteria (1-5) must be met in original description. ‡Z scores were published in an online data supplement to McElhinney et al. (29). §Shown are data for mid trimester fetuses (18 to 32 weeks of age) with severe aortic stenosis associated with a high likelihood of post-natal biventricular repair after fetal intervention (data from McElhinney et al. [29] and Oepkes et al. [10]).

LV = left ventricular.

center and who satisfied the critical elements of the published criteria (**Table 1**) for FCI: decreased left ventricular function, retrograde aortic arch Doppler flow, and left-to-right atrial shunting. The primary outcome for the fetal AS patients was the percentage of infants discharged alive who had biventricular circulation. In the intention-to-treat analysis of all patients, fetal periprocedural demise or late intra-uterine demise counted as "not biventricular."

Although natural history data existed for prenatal prediction of post-natal poor outcome in cases of restrictive interatrial septum (12-14) or for uni-ventricular circulation for pulmonary valve obstruction (15-18), there are no currently accepted criteria for fetal atrial septoplasty, atrial stent placement, or pulmonary valvuloplasty. Thus, fetuses were considered appropriate candidates if they were undergoing FCI or if were not undergoing intervention for noncardiac reasons (e.g., maternal contraindication, patient preference, and others). For atrial procedure candidates, the primary outcome was survival to discharge. For the purposes of reporting of these patients, fetal periprocedural demise or late fetal death counted as a discharge mortality.
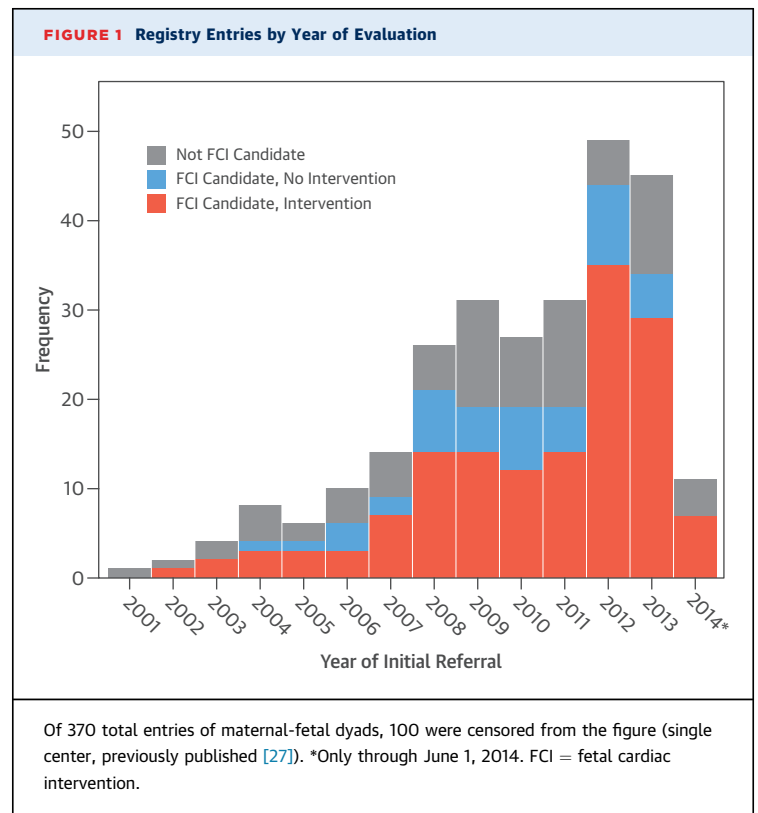
RESULTS

In its first year, the database received entries from 4 institutions, with an additional 4 to 5 new institutions entering data per year for a total of 9 in 2012, 13 in 2013, and 18 in 2014. At the time of this report, there were approximately 60 actively participating individuals and a 37-member steering committee, representing 40 institutions in 15 countries. Six European countries were unable to enter data for FAV procedures due to their concurrent participation in a separate clinical trial.

Two U.S. centers entered only previously published data (currently in the public domain) and were exempt from IRB and data use agreement requirements. One center's regulatory body declined to enter into the data-use agreement despite local IRB approval, and the remainder have active data-use agreements with the IFCIR. All centers obtained local IRB approval or a legal waiver (or both) for the project; additionally, 2 centers required IRB-approved research consent to be signed by patients for the procedure, and 3 centers obtained prospective written consent for data collection from patients at the time of the procedure. Eight centers' local regulations did not require any special consent procedures, as the fetal intervention was considered clinical care.

The total number of cases (FCI and nonintervention) entered each year are shown in **Figure 1**. Eight

institutions entered only intervention cases, 3 entered only nonintervention cases due to FCI not being offered at those locations, and 7 entered all cases presenting, whether FCI was performed or not. Of the institutions entering both types of patients, the lowest FCI rate was 4% and the highest was 85% (median: 42%). Of the 15 centers entering FCI cases, case volume (total, not per year) ranged from 1 to 132; 7 centers reported 3 or fewer cases, 3 reported between 5 and 10 cases, 3 reported 11 to 20 cases, and 2 each reported more than 20 cases. Twelve centers performed FAV, 8 performed FPV, 8 performed atrial septoplasty/septostomy, and 4 performed atrial septal stent procedures. Seven centers had performed only 1 type of procedure, usually FAV.

CASES. At the time of data harvest (June 2014), there were 370 unique records of maternal/fetal dyads in the registry. Forty-one cases that had been previously reported in single-center case reports or small series were included (19-26), including 15 aortic valvulo-plasties, 8 pulmonary valvuloplasties, and 18 atrial septal procedures. One hundred cases of AS from a single institution were subjects of a recent comprehensive report (27) and were censored from the present report to remove overlap and thus facilitate comparison of the IFCIR cohort to that report. Data

FIGURE 1 Registry Entries by Year of Evaluation

Of 370 total entries of maternal-fetal dyads, 100 were censored from the figure (single center, previously published [27]). *Only through June 1, 2014. FCI = fetal cardiac intervention.

TABLE 2   Fetal Cardiac Intervention Registry Patient Entries, Including Basic Demographics

	N	Median GA at Evaluation (range)†	Median GA at Birth (range)	Birth Weight (g)
Total patients referred	370			
Total for this report*	270			
Intervention	145	25 (18-36), n = 145†	38 (29-40), n = 76	2,970 (1,035-4,150), n = 73
No intervention	125	22 (16-38), n = 114‡	38 (27-40), n = 69	2,957 (1,445-4,200), n = 62
Excessive maternal or fetal risk	8			
Pregnancy termination	27			
Maternal contraindication	9			
Not fetal candidate	51			
Chose postnatal care	15			
No reason given	3			

*100 patients from a single center (27) were excluded from this table. †p = 0.01, Mann-Whitney *U* test. ‡p = 0.99 when termination of pregnancy cases (n = 42) were excluded.

FCI = fetal cardiac intervention; GA = gestational age.

regarding fetal gestational age at referral and at birth in the remaining 270 patients are presented in **Table 2**, as are reasons for nonintervention in pregnant women referred for evaluation. The youngest maternal age at which fetal intervention was considered was 16 years of age, but the youngest maternal age recorded for actual FCI was 18 years of age. Nearly one-half of those fetuses evaluated did not undergo FCI, either because they were not deemed candidates by the centers entering the data or the families declined intervention. Maternal contraindications for FCI were cited in 9 cases, and there was a perception of excessive risk to mother or fetus in another 8 cases.

FCI was attempted in 145 patients. Procedural complications and pregnancy outcomes are presented in **Table 3**.

Data regarding FCI access type were missing in 9 entries (3 from a single institution). Of the remaining 136 cases, only a single case done via hysterotomy (in 2002) was recorded. Most cases were performed percutaneously; only 9 women underwent laparotomy or mini-laparotomy, and all but 2 of these occurred prior to 2010; 1 each in 2012 and 2013 were done for AS, both of which were technically unsuccessful despite the laparotomy.

Data regarding FCI maternal/fetal anesthesia type were missing from only 7 cases (3 from 1 institution). Most of the 138 cases in which anesthesia was specified were performed without general anesthesia (n = 109 [79%]), and only 3 of 78 cases (4%) since 2010 have had general anesthesia (the 2 centers that reported general anesthesia use in recent years used it in a minority of their cases). The remainder were done with regional (spinal or epidural [n = 68]), local ([n = 39] type not specified), or both (n = 2) for the mother. All except 4 of the 134 fetuses with data regarding intraprocedural medications (97%) received analgesia, and all of these received neuromuscular blockade.

EXPLORATORY ANALYSES. According to pregnancy and discharge outcomes for all fetuses evaluated for aortic valvuloplasty (**Figure 2**), fetal survival (to live birth only; pregnancy termination and lost to follow-up were excluded) was 80.0% in the FCI group and 85.2% in the non-FCI group. Fetal death was attributed to periprocedural demise more often in the FCI group and to intrauterine demise more commonly in the nonintervention group. Overall neonatal discharge survival (any circulatory status) was 57.5% in the FCI group and 59.3% in the non-FCI group. Among live-born infants, survival to hospital discharge was 75.0% in the technically successful FCI group and 67.7% in the combined non-FCI and technically unsuccessful FCI group.

More fetuses were ultimately discharged alive with biventricular circulation when FCI had been attempted: biventricular circulation in 31.3% (25 of 80 cases) of FCI versus 18.5% (5 of 27 cases) of the non-FCI group. When limited to only live-born infants, the comparison of those with a technically successful intervention versus those in whom there was no FCI or the intervention was technically unsuccessful, there was the suggestion of improved survival to discharge with biventricular circulation: 42.9% (24 of 56) versus 19.4% (6 of 31), respectively.

Of fetuses considered for atrial septal intervention in HLHS, 37 underwent FCI, and 6 were considered candidates but did not undergo intervention (**Figure 3**); no differences were seen in overall discharge survival rates (50% [18 of 36] for FCI vs. 50%

TABLE 3 Pregnancy Outcomes Among FCI Patients by Procedure Type

Parameter	Total	Aortic Valvuloplasty	Pulmonary Valvuloplasty	Atrial Septoplasty With or Without a Stent	Other
Maternal-fetal patients	145	86	16	37	6
GA at intervention (weeks)	26.4 (19.3-36.4)	25.0 (19.3-34.4)	26.0 (23.0-29.6)	30.0 (22.9-36.1)	29.0 (24.6-36.4)
Complications					
Fetal death	16 (11)	10	2	3	1
Bradycardia requiring treatment	47 (32)	29	7	10	1
Hemopericardium requiring drainage	42 (29)	16	9	16	1
Balloon rupture	6 (4)	4	1	1	0
Maternal complication	0				
Pregnancy outcome post-intervention					
Termination	6 (4)	6	0	0	0
Periprocedural demise (<48 h)	9 (6)	5	2	2	0
Late intrauterine demise	2 (1)	1	0	1	0
Term birth	77 (53)	49	5	21	2
Preterm birth (<37 weeks) birth	29 (20)	15	4	8	2
Not stated/in utero	6	0	3	2	1
Survival to first hospital discharge	71 (49)	46	6	18	1

Values are n, median (interquartile range), or n (%).
Abbreviations as in Table 2.

[3 of 6] with no FCI). Comparing only live-born infants following technically successful FCI with live-born infants without fetal procedure success, there were, again, no apparent differences in survival rates: 63.6% (14 of 22) of successful FCI versus 46.7% (7 of 15), respectively, of all others.

Of 30 fetuses considered for FPV, 16 underwent FCI, and 8 met institutional criteria but did not undergo intervention (Figure 4). Of these, 42.9% (6 of 14) of those undergoing FCI and 37.5% (3 of 8) of those without intervention were discharged with biventricular circulation.
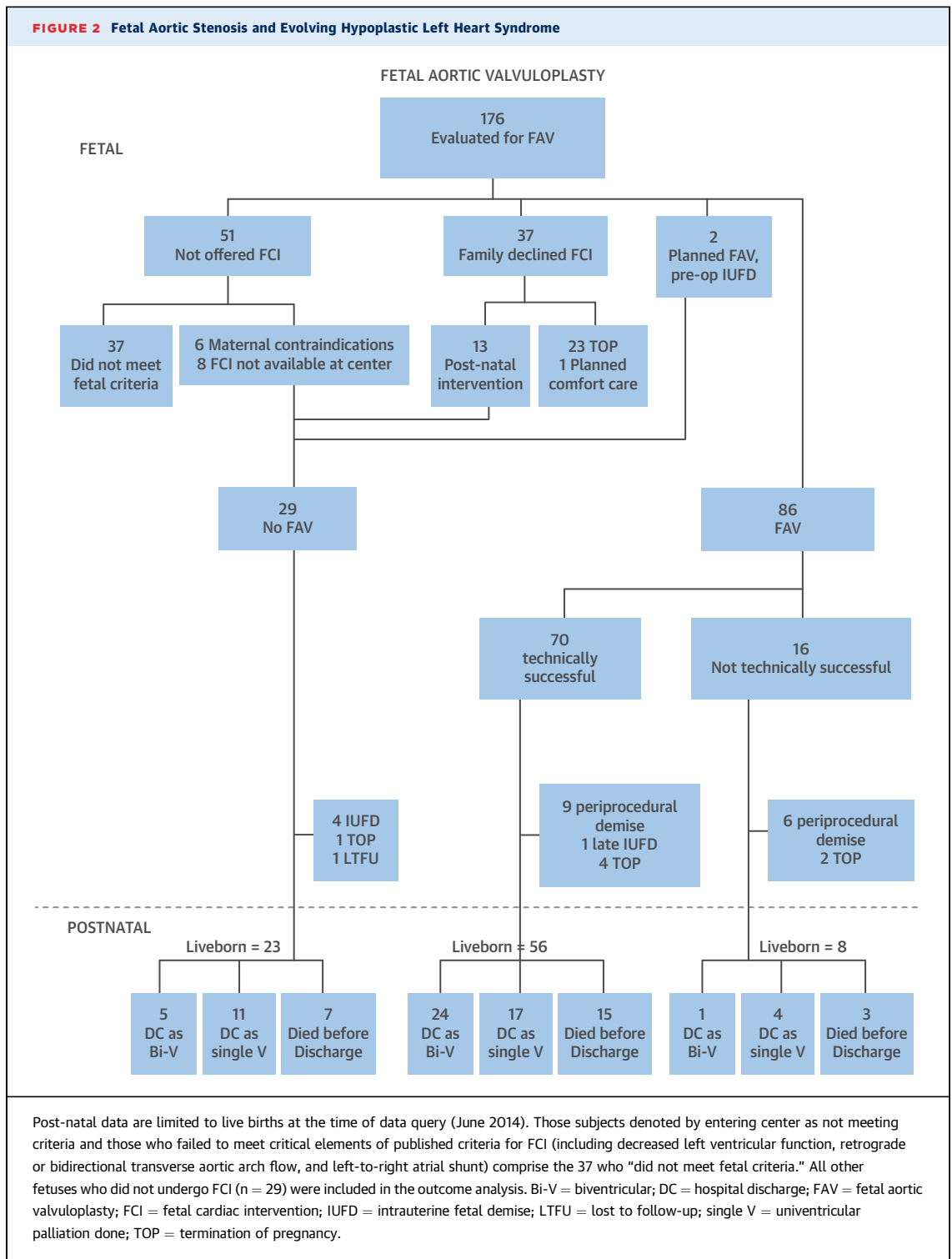
DISCUSSION

Since the initial proposal for the IFCIR in 2010, a robust data collection tool has been created and vetted among the participating institutions. Demographic data including maternal age, ethnicity, country of origin, comorbidities, and gestational age at referral have been systematically collected. Pregnancy and neonatal outcome data including physiological success or failure of fetal procedure with a separate population of referrals who did not ultimately undergo FCI were catalogued and are the subject of this initial report.

Our registry data regarding overall procedure-related complication and loss rates (Central Illustration) are similar to those previously reported in smaller series (28,29). Fetal death during the procedure is not uncommon (11%) and occurred across all procedure types. Additionally, early post-

procedural (<48 h) fetal demise was an issue in this dataset. These rates, which are higher than those previously published in single-center experiences with FCI, likely represent a combination of different learning curves combined with the known complications of any invasive intervention in a compromised fetus (30). Fetal intraprocedural complication rates remain high, with bradycardia and hemopericardium requiring drainage occurring in a significant number of cases and across all procedure types, underlining the need for a team of experienced maternal/fetal, pediatric cardiology, and surgical practitioners whenever these cases are performed. The precise number of procedures and types of personnel needed for a successful center have yet to be determined, but analysis of registry data, including that in the IFCIR, may help us gain insight into the learning curve and the minimum number of cases needed to obtain initial, and maintain ongoing, proficiency (31).

For FAV, technical difficulties were initially the limiting factor, but more recently published procedural success rates are in the 80% range (27). Published data from Austria demonstrated a procedural success rate of 78.6% in more recent years, with procedural success in 10 of 15 fetuses (66.7%) achieving biventricular circulation post-natally (28). Neither the patients in the recently published Boston series (27) nor the Linz series (28) were included in this report (although the Boston patients are in the IFCIR, they were excluded from the original data analysis), allowing valid comparison of these separate cohorts.

FIGURE 2 Fetal Aortic Stenosis and Evolving Hypoplastic Left Heart Syndrome

Post-natal data are limited to live births at the time of data query (June 2014). Those subjects denoted by entering center as not meeting criteria and those who failed to meet critical elements of published criteria for FCI (including decreased left ventricular function, retrograde or bidirectional transverse aortic arch flow, and left-to-right atrial shunt) comprise the 37 who "did not meet fetal criteria." All other fetuses who did not undergo FCI (n = 29) were included in the outcome analysis. Bi-V = biventricular; DC = hospital discharge; FAV = fetal aortic valvuloplasty; FCI = fetal cardiac intervention; IUFD = intrauterine fetal demise; LTFU = lost to follow-up; single V = univentricular palliation done; TOP = termination of pregnancy.

Therefore, it is interesting to note that the biventricular circulation rates noted in our exploratory analysis in the IFCIR (31.3% of all procedural successes; 42.8% of live-born infants with technical success) for fetu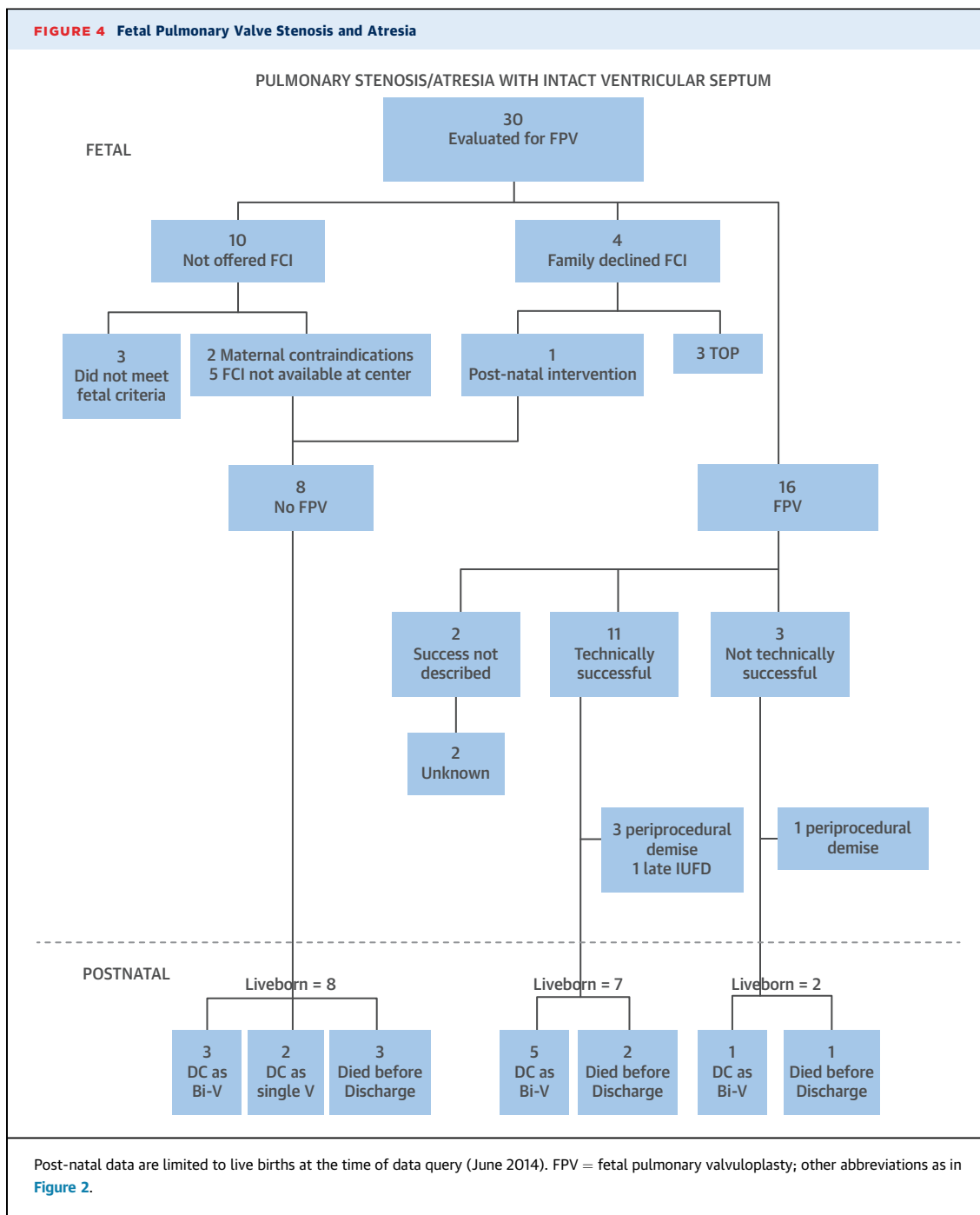ses undergoing aortic valve dilation are similar to those in these single-center series. This suggests that, at least in the hands of experienced fetal medicine centers with appropriate personnel and team-based skill sets for maternal-fetal intervention (and despite likely different approaches to post-natal

FIGURE 3 Fetal Restrictive or Intact Atrial Septum

RESTRICTIVE OR INTACT ATRIAL SEPTUM IN HLHS

FETAL

49 Evaluated for FASI

11 Not offered FCI

6 Did not meet fetal criteria

5 FCI not available at center

1 Family declined FCI for post-natal intervention

6 No FASI

37 FASI

Success not described

1 perforation/dilation

24 Technically successful

15 perforation/dilation
9 stent

12 Not technically successful

3 Unable to position
1 Aborted after FAV
1 perforation/dilation
7 stent

1 Unknown

2 periprocedural demise

3 periprocedural demise

POSTNATAL

Liveborn = 6

Liveborn = 22

Liveborn = 9

3 Survived to DC

3 Died

14 Survived to DC

8 Died

4 Survived to DC

5 Died

Post-natal data are limited to live births at the time of data query (June 2014). FASI = fetal atrial septal intervention; HLHS = hypoplastic left heart syndrome; other abbreviations are as in **Figure 2**.

surgical approaches to borderline patients), similar results can be obtained despite lower procedural volumes. Procedure-related and patient-specific factors that may influence additional confounding are clearly issues that could be further investigated with a more mature dataset using this registry approach. Additionally, analysis of the volume/outcomes relationship will be crucial to answer questions regarding whether these procedures should be centralized to a few institutions worldwide (31).

HLHS with intact or restrictive atrial septum, a variant of HLHS, results in a severely abnormal fetal blood flow pattern, ultimately leading to a significant increase in perinatal mortality despite aggressive post-natal intervention. An initial report of attempts to intervene during fetal life to relieve the obstruction caused by the restrictive atrial septum demonstrated the procedure's technical feasibility but failed to demonstrate a benefit in overall survival (8). More recently, however, the same group showed that

FIGURE 4   Fetal Pulmonary Valve Stenosis and Atresia

Post-natal data are limited to live births at the time of data query (June 2014). FPV = fetal pulmonary valvuloplasty; other abbreviations as in **Figure 2**.

decompression of the left atrium via fetal aortic valvuloplasty or atrial septoplasty may be associated with increased hospital survival (32). Our registry now includes more than 37 patients who had FCI subsequent to the experience published by Marshall et al. (8) in 2004 and several potential "controls"; further analysis of these patients is ongoing and will be the subject of a separate report.

A complex disease spectrum, PS+PA/IVS, is usually associated with various degrees of underdevelopment of the right ventricle. Some centers have reported success with the procedure with post-natal survivors suitable for a 2-ventricle repair (20,25,33). Our registry data confirm the possibility of technical success, but there is no consensus on how to accurately predict the likelihood of a successful biventricular repair in

CENTRAL ILLUSTRATION International Fetal Cardiac Intervention Registry Cases
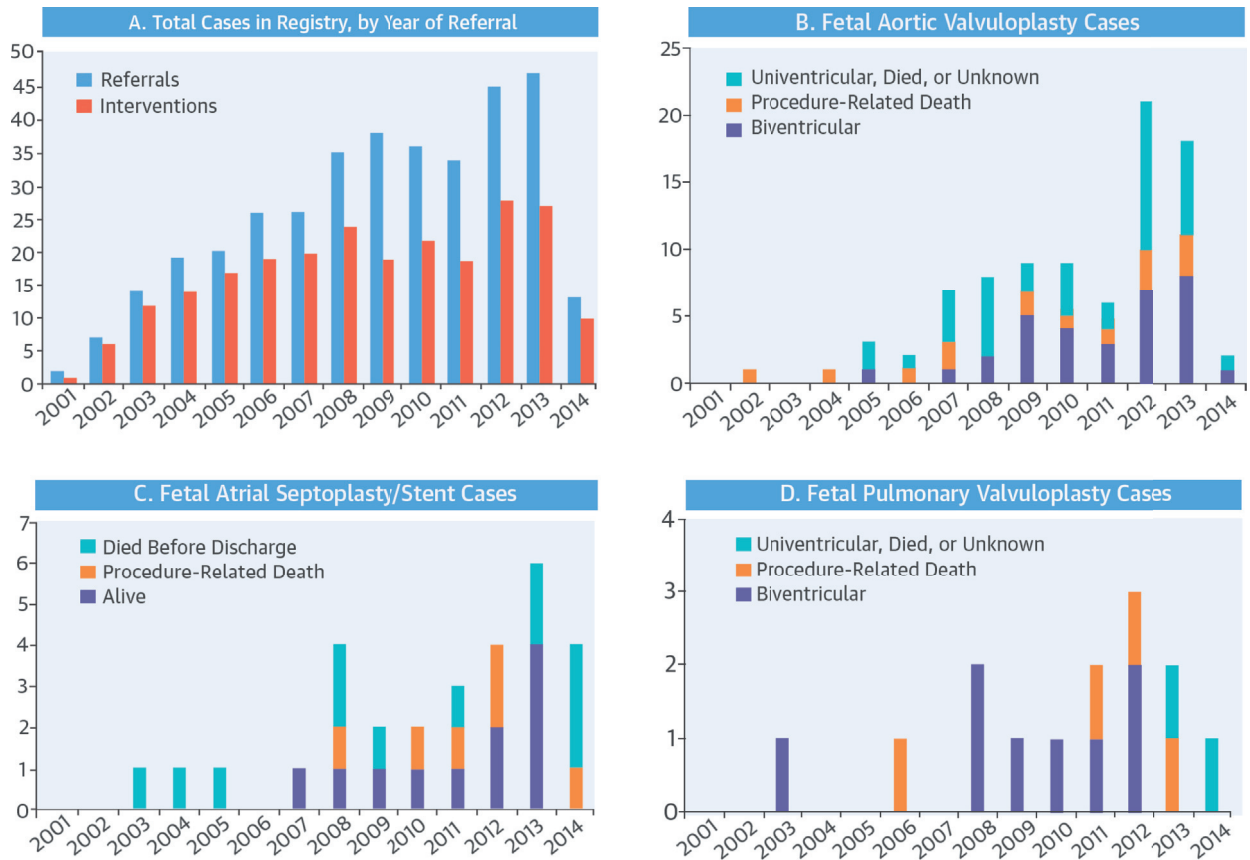
Moon-Grady, A.J. et al. J Am Coll Cardiol. 2015; 66(4):388–99.

With 18 institutions submitting data, the International Fetal Cardiac Intervention Registry includes details of diagnosis, procedures, and outcomes of maternal-fetal dyads, including overall cases **(A)** and those undergoing attempted aortic valvuloplasty **(B)**, septoplasty or stenting **(C)** and pulmonary valvuloplasty **(D)**.

PS+PA/IVS fetuses, and some of the "successful" FCIs may not have been necessary to achieve biventricular outcomes.

Enthusiasm for fetal intervention must be tempered by mindfulness of the interests of the mother and her family, by careful study of the natural history of the disease in untreated human fetuses, and by a willingness to abandon therapy that does not prove effective and safe in properly performed trials. To date, clinical results of maternal/fetal intervention for AS are based on comparisons with historical controls and address efficacy rather than safety (28,29). Many argue that only a properly designed, adequately powered, and meticulously conducted prospective trial, ideally randomized, would sufficiently overcome bias. The counterargument is that, given available data that show in well-selected cases which

patients were highly likely to evolve to HLHS and those who were born with a nearly normal-sized left ventricle after fetal valvuloplasty, denying FCI would be unethical. Collaborative efforts such as the IFCIR may represent a reasonable compromise given a lack of equipoise.

STUDY LIMITATIONS. Although this report provides important information, it also demonstrates the strengths and weaknesses of databases in general and the IFCIR in particular. Registries such as this can help provide information regarding the scope and variety of treatment options, as well as immediate outcomes, in cases of rare diseases; however, the absence of preoperative hemodynamic and uniformly obtained echocardiographic data and long-term follow-up preclude high-quality comparisons among different management strategies. As the

current report serves to provide an initial overview of the IFCIR, the data analysis is largely descriptive. There is only limited ability to infer from and then extrapolate this study's findings beyond a population specifically referred for possible intervention. Another limitation is the suggestion that patients referred for fetal intervention but who ultimately do not undergo FCI may serve as a proper "control" group. Although we present numerical data that might facilitate such comparisons, this limitation should be carefully considered when drawing conclusions from our presentation of intervention versus nonintervention cohorts. Further, because of our referral center-based enrollment and lack of complete follow-up for patients not born at our centers, the registry provides very limited and potentially biased data on post-natal clinical status and any post-natal procedures that may have been performed.

Despite these apparent weaknesses and the lack of standardization, we still have the ability to draw some strong conclusions from the IFCIR database. For example, general anesthesia is essentially no longer used, and all technically successful procedures in the recent era have been done without laparotomy. This illustrates a clear evolution in the field of FCI toward less maternal morbidity.

CONCLUSIONS

Many centers worldwide are conducting FCIs, with the most common procedure being aortic valvuloplasty, although short- and long-term risks and benefits remain largely unclear despite our efforts. Because of the inherent logistical and practical impediments to an international, multicenter, randomized controlled trial, we believe the IFCIR project provides an important resource for those working in this field. The database may help to move the group toward consensus in terms of indication, patient selection, and procedural technique and to establish a minimal procedural dataset addressing outcome parameters. Linkage to pediatric congenital heart surgery and disease databases may be practical and technically feasible and may constitute a valid next step.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Relatively few congenital structural cardiac anomalies are amenable to currently available FCI procedures, which are available in a small number of centers around the world. These invasive procedures have been associated with a high rate of initial technical success and low maternal risk but considerable fetal morbidity and mortality.

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Maternal candidates for fetal cardiac intervention should be informed of the risks and potential complications associated with these invasive procedures and of the uncertainty regarding long-term outcomes for the child.

TRANSLATIONAL OUTLOOK: Future efforts in this international collaboration will focus on evaluating the relationships between procedural volume, short-term clinical outcomes, and longer-term functional and neurodevelopmental status of infant survivors of fetal cardiac procedures.

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KEY WORDS congenital heart defects, fetal cardiac intervention, fetal echocardiography, valvuloplasty

APPENDIX For a complete list of IFCIR contributors and the data sheets, please see the online version of this article.