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Chromosomal Anomalies Influence Parental Treatment Decisions in Relation to Prenatally Diagnosed Congenital Heart Disease

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Abstract

This study aimed to identify the variables that influence parental treatment decisions after a prenatal diagnosis of congenital heart disease (CHD). The authors reviewed all cases of prenatally diagnosed structural CHD from August 1998 to December 2006 at their center. The following variables were studied as potential predictors of parental intent to treat: maternal age, race, insurance status, obstetric history, fetal gender, univentricular versus biventricular cardiac physiology, and fetal chromosomal abnormality. Uni- and multivariable logistic regression analyses were performed. In the review, 252 consecutive cases of prenatally diagnosed CHD were

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identified. Of these, 204 women pursued full medical treatment, whereas 25 women sought termination of pregnancy or comfort care. Parental intent to treat was unknown for 23 cases. Multivariable logistic regression analysis identified fetal chromosomal abnormality as the only variable that influenced parental intent to treat (odds ratio [OR], 14.33; 95% confidence interval [CI], 3.28–62.66; $p = 0.0006$). An associated chromosomal abnormality rather than the severity of the heart defect influences the decision to choose termination of pregnancy or comfort care for a fetus with prenatally diagnosed CHD. Women were 14 times more likely to terminate a pregnancy or seek comfort care for a fetus with CHD if a chromosomal abnormality was present.

Keywords

Chromosomal anomalies; Fetal echocardiography; Prenatal diagnosis

Fetal echocardiography is widely described as a reliable diagnostic tool [2, 7, 16, 17]. Advances in fetal echocardiography have allowed for earlier and more accurate detection of complex cardiac abnormalities. As a result, when congenital heart disease (CHD) is suspected in a fetus, the obstetrician and pediatric cardiologist play an influential role in the prenatal counseling and perinatal planning, a role that will increase as fetal echocardiography continues to become more widely used.

A prenatal diagnosis of CHD is stressful information for parents that generates many difficult questions including the emotive issues of pregnancy termination and comfort care [2, 4, 17, 19]. The roles of the obstetrician and pediatric cardiologist are to provide an accurate diagnosis of the malformation, a clear and truthful picture of the prognosis, an outline of the management and treatment options available, and assistance to parents in reaching the form of management that is best for them [1].

Currently, a sizable body of literature exists that examines the accuracy of fetal echocardiography and its impact on the preoperative condition of the infant and the surgical outcomes [5, 8, 9, 19, 23]. It also is well described that many infants with CHD have extracardiac abnormalities such as visceral heterotaxy and chromosomal defects [4, 7, 11, 16–18]. Termination of pregnancy is reported in the existing literature and, depending on the setting, termination rates among prenatally diagnosed cases of CHD range from 8% to 60% [4, 7, 16, 17, 23]. However, little research has aimed to identify the maternal and fetal factors that have an impact on parental treatment decisions after the prenatal diagnosis of CHD. Effective and thorough prenatal counseling includes an understanding of the issues that influence parental treatment decisions. Therefore, we sought to determine which factors influence parental treatment decisions for a fetus with prenatally diagnosed CHD referred to a regional surgical center.

Materials and Methods

The study population consisted of pregnant women referred to the Medical University of South Carolina (MUSC) for a fetal echocardiogram between August 1998 and December 2006. The Children’s Heart Program of South Carolina based at MUSC in Charleston serves the entire state with four centers located respectively in Charleston, Columbia, Greenville,

and Florence. Since August 1998, the vast majority of fetuses in South Carolina with prenatally diagnosed critical CHD have been referred to MUSC for prenatal evaluation, delivery, and postnatal management.

Critical congenital heart disease was defined as any cardiac structural defect that could potentially require surgical intervention in the first year of life. All patients given a prenatal diagnosis of critical CHD between August 1998 and December 2006 were included in the study. Patients with a prenatal diagnosis of nonstructural heart disease (i.e., fetal arrhythmia) or structural heart disease not requiring surgical intervention in the first year of life were excluded from the study.

A retrospective chart review was performed for all patients undergoing a fetal echocardiogram at MUSC between August 1998 and December 2006. The study received institutional review board approval from MUSC.

The study participants were categorized into two outcome groups: the intent-to-treat group and the intent-not-to-treat group. *Intent not to treat* was defined as the parental decision to seek termination of pregnancy or comfort care.

The maternal and fetal characteristics of the study patients in both outcome groups were reviewed (Table 1). Fetal characteristics examined for potential association with parental treatment intention (to treat or not treat) included gender, chromosomal abnormality confirmed by amniocentesis and/or postnatal testing, and ventricular cardiac physiology (uni- or biventricle). Maternal characteristics included maternal age (years), gravida (1 vs 2 or more), parity (0 vs 1 or more), race (white, black, or other), and insurance status (private vs Medicaid). All patients were insured, and the status “private” included commercial groups, health maintenance organizations, and military insurance. Insurance status was used to classify the socioeconomic group, with Medicaid as a surrogate marker of lower socioeconomic class. Maternal age was treated as a continuous variable in all the analyses, whereas all other variables were treated as categorical variables.

Bivariable associations between maternal and fetal characteristics and parental treatment intention were assessed using Fisher’s exact test for categorical variables and the Wilcoxon rank-sum test for continuous predictors. In addition, univariable logistic regression models with treatment intention as the outcome variable were fitted for each covariate to obtain estimates of unadjusted odds ratios.

Due to patterns of missing data among the covariates, a multivariable regression model based on a complete case analysis substantially reduced the number of intent-not-totreat subjects available for analysis. Therefore, to accommodate multivariable modeling, a multiple imputation model was used to augment missing covariate data with a sequence of Gibbs sampler iterations, as described by van Buuren [20, 21]. Multiple imputation has been shown to produce efficient and unbiased estimates if the data are missing at random [14, 15]. Specifically, the missing quality of being was assumed to be associated possibly with other observed variables but not with the value of the partially observed variable itself.

In our data, missing covariate information was primarily attributable to incomplete medical records, thus satisfying the missing at random assumption. Multivariable models were constructed from the imputation data sets using multiple logistic regression analysis. The fitted models were used to identify independent factors associated with parental intention not to treat. Odds ratio (OR) estimates were obtained as the average across regressions, with corresponding interval estimates reflecting both within-and between-imputation variability.

The number of logistic regression model covariates was limited by the total number of events (subjects with intention not to treat) in the study [12]. Due to the small number of events in this analysis (total of 25), only those maternal and fetal characteristics with attained significance close to nominal α of 0.05 were considered for inclusion in the multivariable model. The functional form of continuous variables was assessed using the method of fractional polynomials [6, 13]. Model fit was assessed on the basis of both the Hosmer and Lemeshow's goodness-of-fit test and the area under the receiving operator characteristic curve.

All statistical tests were two-sided, and type 1 error was controlled for each test at a level of 0.05. Analyses were performed with SAS (version 9.1; SAS Institute, Inc., Cary, NC, USA). Multiply imputed data sets were generated using R (R Development Core Team, R Foundation for Statistical Computing, Vienna, Austria, 2007).

Results

Between August 1998 and December 2006, 252 cases of prenatally diagnosed critical CHD were identified. After 14 pregnancies (5%) ended in fetal demise and 9 families (4%) were lost to follow-up evaluation, 229 subjects were available for the current analysis. Of these 229 subjects, 204 (89%) elected to treat, and 25 (11%) elected not to treat. Among the 25 families that elected not to treat, 14 chose termination of pregnancy and 11 chose comfort care (Fig. 1).

Table 1 summarizes the associations between fetal and maternal characteristics and parental treatment intention. The fetal characteristics that demonstrated a significant difference between the treatment intention groups were chromosomal abnormality ($p < 0.0001$) and biventricular physiology ($p = 0.005$). The maternal characteristics that demonstrated a significant difference between the treatment intention groups were maternal gravida status ($p = 0.047$) and age ($p = 0.005$). Maternal insurance status approached demonstration of a significant difference between the treatment intention groups ($p = 0.055$).

Table 2 summarizes the results of the multiple logistic regression modeling for the 15 multiply imputed data sets. Multivariable analyses showed only chromosomal abnormality to be associated independently with parental treatment preference (OR, 14.33; 95% confidence interval [CI], 3.28–62.66; $p = 0.0006$). Once a prenatal diagnosis of critical CHD was made, a 14-fold increase in the odds of choosing not to treat was observed when a chromosomal abnormality was present.

The following variables for inclusion in the model were considered: chromosomal abnormality, ventricular physiology, maternal age, insurance status, and gravida. Even with

the imputed data, the number of subjects with intention not to treat was small (total of 25 events), resulting in a rate of 5 events per variable in the final 5-variable model. This low event rate precluded investigation of variable interactions and additional assessment of confounding by the remaining fetal and maternal characteristics. The Hosmer and Lemeshow goodness-of-fit test indicated an adequate fit for the multiple logistic regression models fitted to the 15 multiply imputed data sets. Additionally, the average area under the receiving operating characteristic curve across the 15 models was 0.88 (range, 0.85–0.90), indicating that the models' ability to predict treatment preference was good. Some evidence of nonlinearity in maternal age was detected, so the method of fractional polynomials was used to identify optimal transformations [6, 13]. However, maternal age was modeled linearly because no model with transformed age provided a statistically significant improvement in fit.

After chromosomal abnormality was identified as a significant predictor of the parental intent not to treat, the amniocentesis and postnatal chromosome results for the 25 families that chose termination of pregnancy or comfort care were reviewed (Fig. 2). Of the 18 cases with abnormal chromosome results, 16 had a prenatal diagnosis using amniocentesis and two had a postnatal diagnosis.

Among the 14 families that chose termination of pregnancy, 1 had normal amniocentesis results, 10 had abnormal amniocentesis results, and 3 had unknown results because amniocentesis was not performed. Of the abnormal amniocentesis results in the termination group, eight were Trisomy 21, one was Trisomy 18, and one was a complex abnormality with multiple chromosome foci involvement.

Among the 11 families that chose comfort care, 2 were cases of normal chromosomes, 6 were cases of chromosomal abnormality diagnosed prenatally by amniocentesis, 2 were cases of chromosomal abnormality diagnosed postnatally, and 1 case was unknown. Of the abnormal amniocentesis results in the comfort care group, two were Trisomy 13, two were Trisomy 18, one was a partial Trisomy 14, and one was an unbalanced translocation. Both families with normal chromosome results in the comfort care group had fetuses with severe multiorgan abnormalities. One of these pregnancies had conjoined twinning.

Discussion

Counseling parents after a prenatal diagnosis of CHD is an important task for the obstetrician and pediatric cardiologist. In most circumstances, the role of the pediatric cardiologist during the prenatal period is to provide information rather than treatment. The pediatric cardiologist is faced with the challenge of effectively communicating accurate cardiac anatomic details, the need for intervention, and the likely outcomes so that parents are enabled to make fully informed treatment decisions [1, 11].

In the population studied, an associated chromosomal abnormality rather than the severity of the heart defect influenced the decision to choose termination of pregnancy or comfort care for a fetus with prenatally diagnosed CHD. Interestingly, single-ventricle physiology did not affect parental treatment plans. Instead, in the univariable analysis, two-ventricle physiology

was a predictor of the parental decision not to treat. This relationship is most likely due to the confounding effects of Trisomy 21 because most patients with Trisomy 21 have two-ventricle heart disease. The majority of fetuses that were terminated had heart lesions that ordinarily have good surgical outcomes (i.e., atrioventricular septal defect, atrial septal defect, and ventricular septal defect), supporting the observation that chromosomal abnormalities were an important issue for some parents, influencing their treatment decisions.

Early detection of fetal chromosomal abnormalities has several major advantages. First, in the cases with severe heart disease in which the postnatal outcome is expected to be poor, parents may use the data in considering termination of pregnancy. Second, in the cases involving parents who wish to continue with the pregnancy, advanced knowledge of a chromosomal defect allows time for mental and emotional preparation. Parents may enter the postnatal period better equipped to use the multidisciplinary services that a child with a chromosomal defect typically requires. In addition, early knowledge of any chromosomal abnormalities allows the pediatric cardiologist to provide more accurate information regarding the long-term outcomes. This is particularly applicable for infants whose concomitant diagnosis of certain structural heart disease and chromosome abnormality associates them with increased morbidity and mortality [3, 10]. If the diagnosis is determined prenatally, arrangements can be made for these high-risk infants to be delivered at a tertiary care center where pediatric cardiology and cardiac surgery is immediately available. A prenatally detected chromosomal abnormality also enables the pediatric cardiologist to prepare the parents better for possible miscarriage or preterm delivery if there is an increased risk.

Among the 14 families that chose termination of pregnancy, 8 had a prenatal diagnosis of Trisomy 21. It is interesting to note that among the 12 cases of 22q11 deletion, none of the families elected termination of pregnancy or comfort care. However, without knowing the specific details of the prenatal counseling sessions, it is not possible to determine why such decisions were made.

The impact of gestational age at the time of diagnosis could not be included in our statistical analysis because many of the mothers had received a preliminary diagnosis at an earlier gestational age by their local obstetrician or cardiologist. Referrals to our institution for confirmatory diagnosis and establishment of tertiary care often occurred after 24 weeks gestation. The mean gestational age at diagnosis was 27.6 weeks. It is unclear whether the late referrals reflected a parent’s decision to decline termination of pregnancy or whether the cardiac anomaly simply was not detected until a later gestational age.

This study had several limitations. It was a retrospective, single-center study. The characteristics of this study population may have been specific to our medical center and not representative of the larger national or international population. Because the population in South Carolina is predominantly conservative socially and politically, the study subjects may have been more likely to decline termination of pregnancy than patients at other centers. Some potentially important variables such as gestational age at the time of the initial

diagnosis, religion, marital status, and whether the pregnancy was planned were not available for analysis.

The potential bias introduced during counseling was not included because it could not be measured retrospectively. Furthermore, many of our patients received counseling from several different individuals (primary obstetrician, high-risk obstetrician, geneticist, and pediatric cardiologist), making it difficult to assess the influence of one individual counselor accurately. Although late referrals and diagnosis can limit the number of terminated pregnancies, it should not have limited the number of cases of comfort and palliative care.

A small possibility exists that false-positive prenatal chromosome analysis may have resulted in termination. However, the likelihood of this occurring is low given that the reported accuracy of amniocentesis and chorionic villus sampling exceeds 99% [22].

In conclusion, fetal chromosomal abnormality appears to be an important issue for parents after they have received a prenatal diagnosis of CHD. In this study, an associated chromosomal abnormality was more likely to result in termination of pregnancy or in comfort care than the severity of the structural heart defect. Approximately 60% of the families that chose termination of pregnancy had a fetus with a prenatal diagnosis of Trisomy 21. Amniocentesis serves an important role of facilitating informed parental decisions after a prenatal diagnosis of CHD and should be offered to every family in the prenatal counseling session. Additionally, follow-up counseling after the amniocentesis is necessary to ensure that parents are appropriately and accurately informed about the abnormalities and anticipated outcomes.

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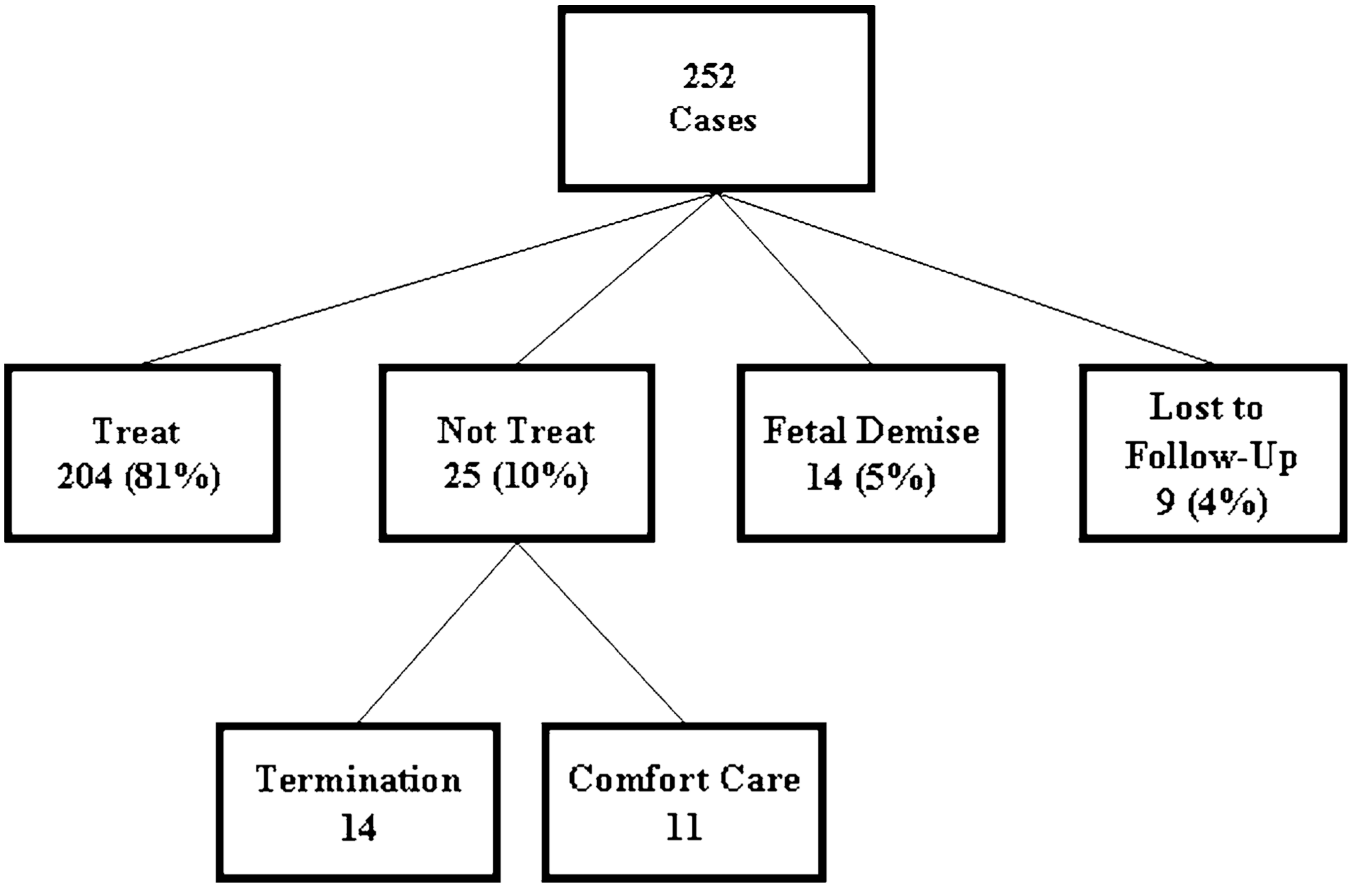

Fig. 1.

Parental treatment intention in 252 consecutive cases of prenatally diagnosed critical congenital heart disease between August 1998 and December 2006

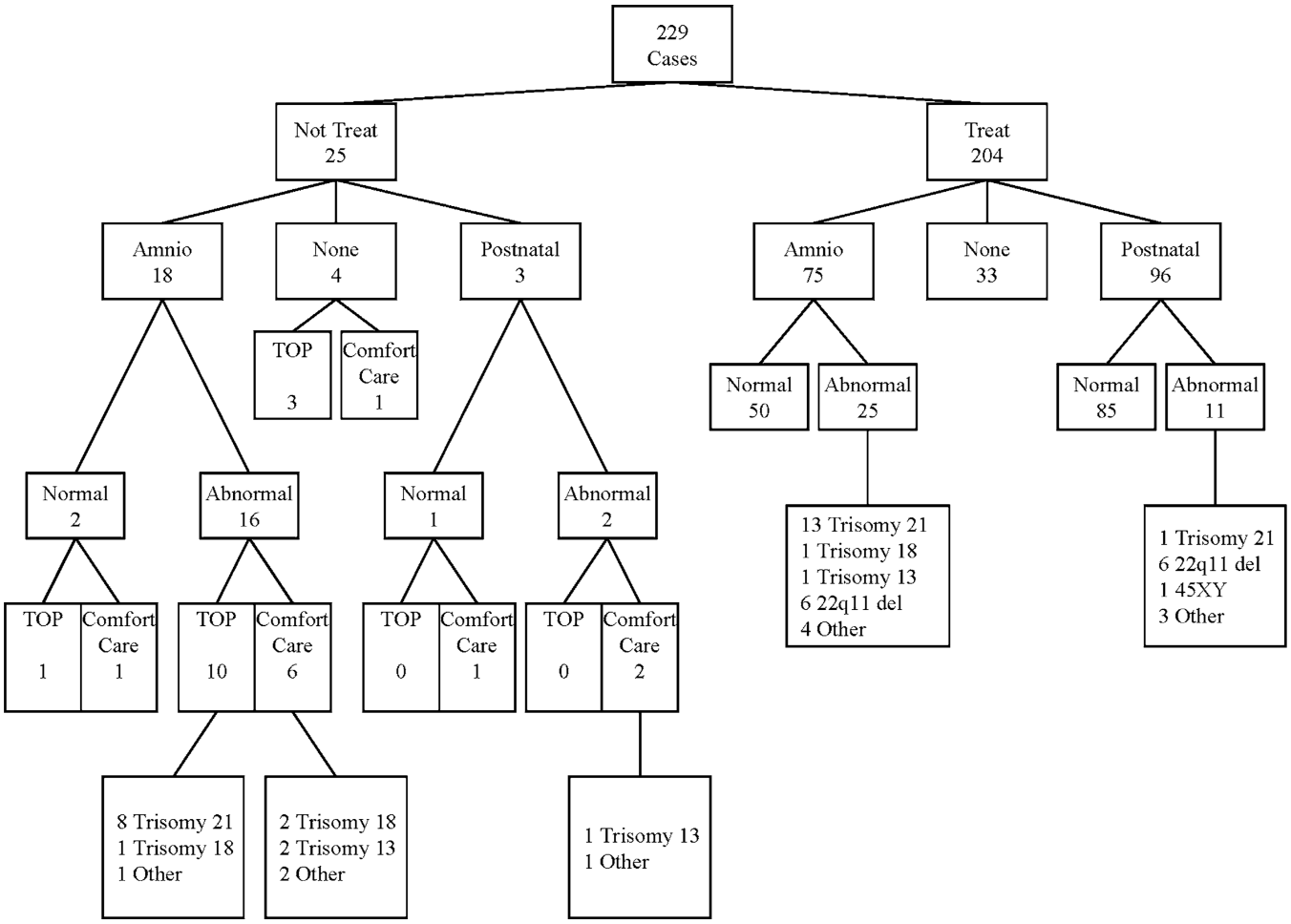

Fig. 2.

Amniocentesis and postnatal chromosome results for 229 cases of prenatally diagnosed critical congenital heart disease in which parental treatment intention was identified. *amnio* amniocentesis, *postnatal* postnatal chromosome testing, *TOP* termination of pregnancy

Table 1

Summary of bivariable associations between fetal and maternal characteristics and parental treatment intention

Variable	Level	Treatment intention[a]		*p* value[b]
		Not treat (*n* = 25)	Treat (*n* = 204)	
Fetal characteristics				
Gender				0.80
	Male	10 (8)	122 (92)	
	Female	8 (9)	81 (91)	
Chromosomal abnormality				<0.0001
	No	3 (2)	135 (98)	
	Yes	18 (33)	36 (67)	
Ventricular physiology				0.0047
	Univentricular	4 (4)	108 (96)	
	Biventricular	16 (15)	94 (85)	
Maternal characteristics				
Race				0.63
	Caucasian	14 (10)	121 (90)	
	African-American	7 (10)	62 (90)	
	Other	4 (17)	20 (83)	
Insurance				0.055
	Medicaid	8 (7)	108 (93)	
	Private	17 (15)	93 (85)	
Gravida				0.047
	1	1 (2)	52 (98)	
	2+	17 (12)	127 (88)	
Parity				0.62
	0	6 (7)	76 (93)	
	1+	12 (10)	103 (90)	
Age (years)[c]		31 (27–37)	27 (22–33)	0.0051

[a] Values for categorical variables are frequencies (%). Values reported for age are median (interquartile range) due to skewness in the distribution of maternal age. Some frequencies summed across levels of categorical variables do not total 25 for intention not to treat and 204 for intention to treat due to missing values

[b] *p* values for categorical variables were calculated using Fisher's exact test; *p* value for age was calculated using the Wilcoxon rank-sum test

[c] Seven intent-to-treat subjects had missing values for maternal age

Table 2

Summary of univariable (unadjusted) and multivariable (adjusted) logistic regression analyses

Variable	Unadjusted[a]		Adjusted[b]	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Chromosomal abnormality	22.49 (6.28, 80.59)	<0.0001	14.33 (3.28, 62.66)	0.0006
Biventricle physiology	4.60 (1.49, 14.23)	0.0082	1.56 (0.41, 5.93)	0.51
Maternal age[c]	1.47 (1.11, 1.96)	0.0075	1.09 (0.74, 1.62)	0.65
Gravida 2+	6.96 (0.90, 53.64)	0.063	1.28 (0.37, 1.40)	0.28
Private insurance	2.47 (1.02, 5.99)	0.045	2.01 (0.64, 6.34)	0.23

OR odds ratio, CI confidence interval

[a] Univariable logistic regression models were fitted based on a complete case analysis of the original data

[b] Multivariable logistic regression analysis was based on 15 data sets, with missing data multiply imputed. OR and corresponding 95% CI reflect both within- and between-imputation variability

[c] Odds ratio for maternal age is for a 5-year increase