The marked advances in cardiac surgery in recent decades have resulted in an increased number of survivors with congenital heart disease (CHD), with the number of adult patients in Japan with CHD estimated to be >400,000; as a result, many women with CHD reach childbearing age.1-3 Hence, pregnancy and delivery in female patients with either unrepaired or repaired CHD are of critical concern for cardiac health providers. During pregnancy, maternal physiologic adaptations in

**Background:** Although advances in cardiac surgery have led to an increased number of survivors with congenital heart disease (CHD), epidemiological data regarding the pregnancies and deliveries of patients with repaired CHD are scarce.

**Methods and Results:** In this study, we retrospectively reviewed the clinical outcomes of pregnancies and deliveries of women with repaired CHD. Overall, 131 women with repaired CHD were enrolled and there were 269 gestations. All patients were classified as New York Heart Association (NYHA) Class I or II. The prevalence of cesarean sections was higher in patients with (CyCHD) than without (AcyCHD) a past history of cyanosis (51% vs. 19%, respectively; P<0.01). There were 228 offspring from 269 gestations and the most prevalent neonatal complication was premature birth (10%), which was more frequent in the CyCHD than AcyCHD group (15.7% vs. 5.6%, respectively; P<0.01). Five maternal cardiac complications during delivery were observed only in the CyCHD group (8%); these were classified as NYHA Class II and none was fatal.

**Conclusions:** Delivery was successful in most women with repaired CHD who were classified as NYHA Class I or II, although some with CyCHD and NYHA Class II required more attention. Cesarean sections were more common in the CyCHD than AcyCHD group, and CyCHD may be a potential risk for preterm deliveries.

**Key Words:** Adult congenital heart disease; Cesarean section; Premature; Tetralogy of Fallot

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Pregnancy and Delivery in Patients With Repaired Congenital Heart Disease
— A Retrospective Japanese Multicenter Study —

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the circulatory system include progressive increases in cardiac output, sodium and water retention, and a reduction in systemic vascular resistance. In female patients, residual lesions of CHD may have deleterious effects on the health of both the mother and fetus during pregnancy. The management of pregnancy in patients with CHD should be multidisciplinary to minimize maternal morbidity and mortality. In addition to maternal cardiac adverse events, physicians should consider potential risks to the fetus, which can include prematurity and growth retardation.

Studies have investigated the predictors of complications during pregnancy in women with cardiovascular disease. Pregnancy can be challenging for some patients with cyanotic CHD, because they could be at risk of hypoxemia, heart failure, arrhythmia, and teratogenicity resulting from cardiovascular drugs. In addition, cardiac complications, which can include worsening of New York Heart Association (NYHA) functional class, pulmonary hypertension, and residual cyanosis may worsen maternal and fetal outcomes. Although there are guidelines for the indication and management of pregnancies and deliveries in women with heart disease, few studies have evaluated the outcome of pregnancies and deliveries in clinically stable patients who have already received intracardiac repairs for CHD. The aim of this study was to determine maternal and fetal outcomes in women with repaired CHD and preserved cardiac function.

**Methods**

**Patients and Controls**

The present study was a retrospective cohort study conducted by the Committee for Genetics and Epidemiology of Cardiovascular Disease in the Japanese Society of Pediatric Cardiology and Cardiac Surgery. Clinical data were collected between January 2009 and December 2014 from pregnant women with CHD. Questionnaires regarding maternal and fetal outcomes in pregnant patients with CHD were sent to collaborating facilities. Data collected included demographics, cardiac diagnoses, current cardiac medications, maternal age, gravidity, parity, delivery history, and maternal and fetal outcomes of patients with repaired CHD or residual lesions after cardiac repair. Patients with un repaired CHD, univentricular physiology, pulmonary hypertension, and NYHA Class III or IV were excluded from the study.

Study patients were classified clinically into 2 groups based on their past history of cyanosis, one group with acyanotic CHD (AcyCHD) and the other with cyanotic CHD (CyCHD). The AcyCHD group was defined as having simple cardiac defects, including ventricular septal defect (VSD), atrial septal defect (ASD), atrioventricular septal defect, pulmonary stenosis, patent ductus arteriosus, and coarctations of the aorta (COA). CyCHD included any anatomical lesion with cyanosis, such as tetralogy of Fallot (TOF).

This study was reviewed and approved by a Central Ethics Board at Tokyo Women’s Medical University (Approval no. 3437), confirming that the study conformed to the tenets of the Declaration of Helsinki and the ethical standards of the responsible committee on human experimentation.

**Statistical Analyses**

The significance of differences in clinical variables between patients with AcyCHD and CyCHD was evaluated using the \( \chi^2 \) test, Student’s t-test, or the Mann-Whitney U-test. Categorical values are expressed as percentages, whereas continuous variables are presented as the median with range (minimum–maximum). Two-sided P<0.05 was considered statistically significant. Statistical analyses were performed using Statmate IV for Windows (Atoms, Tokyo, Japan).

**Results**

**Patient Characteristics**

Data were collected from 8 institutions and analyzed. The pediatric cardiology divisions in these institutions are constantly managing the pregnancy and delivery of patients with adult CHDs, and the institutions are considered to be representative of institutes in Japan.

Overall, 131 patients with repaired CHD were enrolled in the study (70 AcyCHD and 61 CyCHD patients; Table 1). In the AcyCHD group, VSD was the most common lesion (observed in 34 of 70 patients; 49%), followed by ASD in 13 patients (19%), and COA in 10 patients (14%). In the CyCHD group, TOF was the most commonly observed lesion (34/61; 56%). None of these patients with repaired CHD had residual cyanosis. Of the 131 patients, 113 (86%) were NYHA Class I and the remaining 18 (14%) were NYHA Class II. Oral medications for CHD were prescribed for 22 of 131 patients (17%); 6 in the AcyCHD group and 16 in the CyCHD group. Angiotensin-converting enzyme inhibitor; AcyCHD, history of acyanotic congenital heart disease (CHD); CyCHD, history of cyanotic CHD; NYHA, New York Heart Association.
enzyme inhibitors (ACEIs) were used in 3 patients, but the use of ACEIs stopped in all CyCHD patients during pregnancy because the teratogenicity of ACEIs is contentious.

**Pregnancies**
The median age at the time of the last pregnancy was 31 years (range 18–43 years) and there was no significant difference in median age at last pregnancy between the AcyCHD and CyCHD groups. In all, 131 patients had 269 pregnancies (147 in the AcyCHD group and 122 in the CyCHD group). Of these 269 pregnancies, there were 31 miscarriages (12%) in 26 patients, including 10 elective terminations (4%) in 7 patients. There were no significant differences between the AcyCHD and CyCHD groups in the frequency of miscarriages (10% vs. 14%, respectively; P=0.34) or terminations (5% vs. 2%, respectively; P=0.22; Table 2).

**Deliveries**
In all, there were 228 deliveries among the 269 pregnancies (126 in the AcyCHD group and 102 in the CyCHD group), and all the deliveries were singletons. Of these 228 deliveries, 152 (67%) were vaginal deliveries, with cesarean sections performed in the remaining 76 (33%) because of maternal cardiac complications and obstetric reasons, such as breech presentation. Cesarean sections were more common in the CyCHD than AcyCHD group, and this difference was statistically significant (51% vs. 19%, respectively; P=0.0001; Table 2).

**Offspring**
Of the 269 pregnancies, 228 (85%) resulted in a live birth (126 in the AcyCHD group and 102 in the CyCHD group). The mean number of offspring for patients with CHD was 1.74. The most common neonatal complication was premature birth, which was observed in 23 of 228 (10%) deliveries and was significantly more frequent in the CyCHD than AcyCHD group (15.7% vs. 5.6%, respectively; P=0.015; Table 3). Twelve of 228 neonates (5.2%) were reported to have CHD, and although the frequency of CHD in offspring was somewhat higher in patients with CyCHD than with AcyCHD, the difference did not reach statistical significance (6.9% vs. 5%, respectively; P=0.77; Table 3).

**Maternal Outcomes**
In this study, 5 maternal cardiac complications were noted only in the CyCHD group (8%; Table 4). All 5 women belonged to NYHA Class II, and 2 of these 5 patients received oral medications for CHD during their pregnancies. Two patients with TOF experienced maternal heart failure and miscarriages. One woman with TOF had 2 abnormal deliveries, one a cesarean section and the other a miscarriage. During her first pregnancy, this woman miscarried during the first trimester. During the second pregnancy, the woman underwent a cesarean section because of maternal heart failure. The remaining 3 patients with maternal cardiac complications underwent cesarean sections and thereafter required hospitalization due to postpartum heart failure. A new-onset arrhythmia during

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**Table 2. Obstetric Outcomes**

<table>
<thead>
<tr>
<th></th>
<th>Total (n=135)</th>
<th>AcyCHD (n=70)</th>
<th>CyCHD (n=61)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (range) age at last pregnancy &lt;years&gt;</td>
<td>31.0 (18–43)</td>
<td>31.5 (19–42)</td>
<td>31.0 (18–43)</td>
<td>0.44</td>
</tr>
<tr>
<td>No. pregnancies</td>
<td>269</td>
<td>147</td>
<td>122</td>
<td></td>
</tr>
<tr>
<td>No. births</td>
<td>228 (85)</td>
<td>126 (86)</td>
<td>102 (84)</td>
<td>0.74</td>
</tr>
<tr>
<td>Miscarriage</td>
<td>31 (12)</td>
<td>14 (10)</td>
<td>17 (14)</td>
<td>0.34</td>
</tr>
<tr>
<td>Termination</td>
<td>10 (4)</td>
<td>7 (5)</td>
<td>3 (2)</td>
<td>0.22</td>
</tr>
<tr>
<td>No. successful deliveries</td>
<td>228</td>
<td>126</td>
<td>102</td>
<td></td>
</tr>
<tr>
<td>Vaginal</td>
<td>152 (67)</td>
<td>102 (81)</td>
<td>50 (49)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Cesarean section</td>
<td>76 (33)</td>
<td>24 (19)</td>
<td>52 (51)</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Unless indicated otherwise, data are given as n (%). P values are for differences between the acyanotic congenital heart disease (AcyCHD) and cyanotic congenital heart disease (CyCHD) groups.

**Table 3. Offspring Outcomes**

<table>
<thead>
<tr>
<th></th>
<th>Total (n=135)</th>
<th>AcyCHD (n=70)</th>
<th>CyCHD (n=61)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. live births</td>
<td>228</td>
<td>126</td>
<td>102</td>
<td></td>
</tr>
<tr>
<td>No. premature births (%)</td>
<td>23 (10)</td>
<td>7 (5.6)</td>
<td>16 (15.7)</td>
<td>0.015</td>
</tr>
<tr>
<td>No. neonates with CHD (%)</td>
<td>12 (5.2)</td>
<td>6 (5)</td>
<td>6 (6.9)</td>
<td>0.77</td>
</tr>
<tr>
<td>CHD in neonate/mother's CHD (n)</td>
<td>ASD 2/ASD 1</td>
<td>TOF 3/TOF 2, PTA 1</td>
<td>VSD 1/VSD 1</td>
<td>VSD 1/TOF</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

P values are for differences between the acyanotic congenital heart disease (AcyCHD) and cyanotic congenital heart disease (CyCHD) groups. ASD, atrial septal defect; COA, coarctation of the aorta; CHD, congenital heart disease; DORV, double-outlet right ventricle; PS, pulmonary stenosis; PTA, persistent truncus arteriosus; TOF, tetralogy of Fallot; VSD, ventricular septal defect.
delivery was observed in a patient with double-outlet right ventricle (DORV). None of these 5 patients had a fatal event because of their complications.

**Discussion**

This study investigated maternal and fetal outcomes following pregnancy in patients with repaired CHD categorized as NYHA Class I or II. Most women tolerated pregnancy and delivery, but approximately one-third of patients categorized as NYHA Class II (5/18; 28%) were hospitalized due to heart failure or arrhythmia during pregnancy, although none of these events was fatal. Of note, all these patients had repaired CyCHD. Several studies investigated the predictors for cardiac complications in patients with CHD during pregnancy and reported that maternal outcomes were dependent on the severity of their CHD.\(^5\)\(^7\) Numerous studies have reported that an advanced NYHA functional class, a history of medication for CHD, systemic and pulmonary hypertension, residual cyanosis, left-sided cardiac obstructive lesions, and single ventricular physiology are associated with adverse cardiac events in patients with CHD regardless of surgical repair.\(^5\)\(^7\)\(^10\) The findings of the present study highlight that hemodynamically stable patients with repaired CHD can tolerate pregnancy, but suggest that attention needs to be paid to some women with repaired CyCHD in NYHA Class II for adverse cardiac events during pregnancy even though they appear to be stable in the non-pregnant state.

In this study, the rate of miscarriages was similar in the AcyCHD and CyCHD groups. The rate of miscarriages in the present study was 12\%, which is similar to that across all pregnancies in the general Japanese population (rate ~10–15\%).\(^13\) but slightly lower than that in patients with CHD (reportedly 12–18\% of all pregnancies).\(^6\)\(^14\) As mentioned above, the overall maternal outcome in this study was substantially better than reported previously.\(^7\)\(^11\)\(^12\)\(^15\) The better outcomes in this study are likely due to the fact that we excluded patients with advanced NYHA functional class ratings, univentricular hearts, and pulmonary hypertension, all of which are associated with increased maternal morbidity and mortality.\(^9\)\(^16\)\(^17\)

However, compared with AcyCHD patients, those with CyCHD often experienced cesarean sections for cardiac complications, premature deliveries, and heart failure, with the differences between the 2 groups in these parameters being statistically significant. In the present study, more than half the patients with CyCHD had repaired TOF. The potential risk of heart failure during pregnancy has been reported in patients with repaired TOF,\(^18\) suggesting that right ventricular volume overload due to pulmonary regurgitation may worsen during pregnancy and eventually result in maternal and fetal complications. Even though patients with well-repaired TOF may never have had ventricular dysfunction or prior arrhythmias, clinical or subclinical right ventricular failure may develop when preload is increased due to an increase in plasma volume during pregnancy. Physicians should consider a maternal history of cyanosis as a potential risk factor for maternal and fetal morbidity during pregnancy. This is the first study to report that women with repaired CyCHD and NYHA Class I or II may be at potential risk of cesarean sections and preterm deliveries, whereas previous studies primarily focusing on the potential risk in patients with more severe disease.\(^15\)\(^19\)

There were 10 elective terminations among the 269 pregnancies (4\%) in 7 patients. The reasons for the elective terminations are unknown because the questionnaire used in this study did not ask for reasons. We speculate that, in addition to cardiac reasons, there may have been social reasons why patients chose to undergo an elective termination because some of the terminations were performed in clinically stable women.

In this study 5.2\% of newborns had CHD, which is consistent with previous reports,\(^15\) and the frequency of CHD did not differ significantly between the AcyCHD and CyCHD groups. Physicians should inform patients that the risk of CHD in newborns in the case of a maternal history of CHD is somewhat higher than in women without such a history.\(^20\)

This study does have some limitations. First, the data were derived from only 8 institutions because of the low response rate to the questionnaires, even though the institutions responding to the survey are representative of institutions across Japan. Second, there were differences in the rates of cesarean sections among institutions, which may reflect potential differences in the indications for cesarean sections at each institution and could be a bias or confounder. However, in the present study the rate of cesarean sections was consistently greater in the CyCHD than AcyCHD group in all 8 institutions (data not shown), suggesting that the differences in the rate of cesarean sections between the CyCHD and AcyCHD groups are unlikely to have resulted from the indications for cesarean sections in each institution. Despite these limitations, this study, which was conducted by the Committee for Genetics and Epidemiology of Cardiovascular Disease in the Japanese Society of Pediatric Cardiology and Cardiac Surgery, is the first Japanese nationwide cohort study describing pregnancy and delivery in patients with repaired CHD.

**Table 4. Adverse Events in 5 Pregnant Patients With Cyanotic CHD**

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>CHD</th>
<th>Age at last delivery (years)</th>
<th>No. pregnancies</th>
<th>No. live births</th>
<th>No. abnormal deliveries</th>
<th>NYHA class</th>
<th>Medication during pregnancy</th>
<th>Adverse event</th>
<th>Type of abnormal delivery</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TOF</td>
<td>31</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>II</td>
<td>–</td>
<td>HF</td>
<td>Miscarriage</td>
</tr>
<tr>
<td>2</td>
<td>TOF</td>
<td>35</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>II</td>
<td>+</td>
<td>HF</td>
<td>Miscarriage, CS</td>
</tr>
<tr>
<td>3</td>
<td>DORV</td>
<td>24</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>II</td>
<td>–</td>
<td>HF</td>
<td>CS</td>
</tr>
<tr>
<td>4</td>
<td>DORV</td>
<td>32</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>II</td>
<td>+</td>
<td>HF</td>
<td>CS</td>
</tr>
<tr>
<td>5</td>
<td>DORV</td>
<td>35</td>
<td>4</td>
<td>3</td>
<td>4</td>
<td>II</td>
<td>–</td>
<td>Arrhythmia</td>
<td>CS (3 times), miscarriage</td>
</tr>
</tbody>
</table>

+, patient received medication; –, patient did not receive medication; CHD, congenital heart disease; CS, cesarean section; DORV, double-outlet right ventricle; HF, heart failure; NYHA FC, New York Heart Association; TOF, tetralogy of Fallot.
Conclusions
Although delivery was successful in most women with repaired CHD and NYHA Class I or II, there was a high prevalence of cesarean sections in those with repaired CyCHD. In addition, a history of CyCHD may be a potential risk factor for preterm deliveries.

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None of the authors has any conflicts of interest to disclose.

IRB Information
This study was approved by the Medical Ethics Committee of Tokyo Women’s Medical University (Clinical Study #3437).

References