Outcome of Pregnancy and Effects on the Right Heart in Women With Repaired Tetralogy of Fallot

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Background: Improved medical techniques have allowed most women with repaired tetralogy of Fallot (TOF) to reach childbearing age. The predictors of adverse events and the effects of pregnancy on cardiac function have not been clearly described in these patients.

Methods and Results: In the present study we retrospectively reviewed 40 deliveries in 25 patients with repaired TOF. There were 23 patients in New York Heart Association (NYHA) class I, and 2 in classes II–III before pregnancy. The mean age at delivery was 29.1 years and the mean gestational period was 37.8 weeks. Seven pregnancies (17.5%) in 7 patients were complicated with cardiac events such as a decline in NYHA class and arrhythmia. History of ablation and the baseline cardiothoracic ratio on chest radiography were predictors of adverse events. Peak plasma brain natriuretic peptide (BNP) level after the second trimester was higher in patients with cardiac events. Left ventricular size and contraction did not change from before to after pregnancy, but the right ventricle was enlarged at 6 months after delivery.

Conclusions: Many of the pregnancies in women with repaired TOF were successful. However, careful management is required for some patients and the BNP level may be a useful marker to identify these patients. Because the right heart tended to be enlarged in the late postpartum period, pregnancy may also affect the long-term prognosis of patients with repaired TOF. (Circ J 2012; 76: 957–963)

Key Words: Arrhythmia; Congenital heart disease; Heart failure; Outcomes; Pregnancy

Tetralogy of Fallot (TOF) is the most common cyanotic congenital heart disease, and is characterized by a large ventricular septal defect (VSD), right ventricular outflow tract obstruction, right ventricular hypertrophy, and overriding of the aorta. Improvements in medical and surgical treatment have permitted most female patients with TOF to reach childbearing age after intracardiac repair. Several reports have shown relatively favorable pregnancy outcomes among such patients, although with adverse maternal events associated with left ventricular dysfunction, severe pulmonary hypertension, and severe pulmonic regurgitation with right ventricular dysfunction. However, few studies have analyzed the pregnancy-associated risks in these patients using physiological and radiological examinations, including evaluation of persistent cardiac changes after each pregnancy. Therefore, the aims of this study were (1) to characterize the risk factors for pregnancy-associated cardiac events, and (2) to evaluate the long-term effects of pregnancy on the heart in women with repaired TOF.

Methods

Patients

We retrospectively reviewed a series of 25 pregnant women with repaired TOF who delivered at the National Cerebral and Cardiovascular Center from 1987 to April 2010. Data were obtained from medical records. The 25 subjects had a total of 40 deliveries. Spontaneous or elective abortions were excluded from the study population. Baseline data were obtained for age, basic cardiac anatomy, history of prior surgery, cardiac events, medications, and smoking habit. New York Heart Association (NYHA) functional class, results from chest radiography, ECG, transthoracic echocardiography, and the plasma brain natriuretic peptide (BNP) level were reviewed from 1...
year before pregnancy to 1 year after delivery.

Outcomes
Cardiac events were defined as new onset or worsening of arrhythmia requiring treatment, heart failure (a decline in NYHA class, pulmonary congestion confirmed by chest radiography, requirement for diuretic therapy), endocarditis, or thromboembolic events during pregnancy to 1 month after delivery. Obstetric events were defined as pregnancy-induced hypertension (PIH: systolic blood pressure (BP) ≥140 mmHg or diastolic BP ≥90 mmHg after 20 weeks of gestation), premature labor (labor before 37 weeks of gestation), and postpartum hemorrhage (blood loss in vaginal delivery ≥800 ml or in cesarean delivery (CS) ≥1,500 ml). Offspring events were defined as small-for-gestational-age (SGA, birth weight <10th percentile), complication with congenital heart disease, and intrauterine or neonatal death (within 28 days). To analyze the risk factors for pregnancy-associated cardiac events, we compared the latest pregnancy between patients with and without cardiac events.

Physical Examinations
Results of chest radiography and ECG performed within 1 year before pregnancy to the first trimester (until 13 weeks of gestation) were used as baseline data. Cardiorespiratory ratio (CTR) and QRS duration were measured. Patients with pacemaker rhythm were excluded from the assessment of QRS duration on echocardiography. The patients were routinely examined by transthoracic echocardiography by 2 skilled ultrasonographers who were in charge of obstetric patients and were blinded to the study. We obtained echocardiographic data on 4 occasions: (1) within 1 year before pregnancy to the first trimester, (2) in the second and third trimester (from 14 weeks of gestation to delivery), (3) after delivery to 1 month postpartum, and (4) from 6 months to 1 year after delivery. Patients who started diuretics during their pregnancy were excluded from the comparison of echocardiographic changes among these 4 periods.

Ventricular dimensions, such as left ventricular end-diastolic diameter (LVDd), left ventricular end-systolic diameter (LVDs), and right ventricular end-diastolic diameter (RVDd), were measured from M-mode echocardiography in the parasternal long- or short-axis views. Percent fractional shortening (%FS) was calculated from the LVDd and LVDs. Right ventricular size was graded retrospectively as normal or mildly, moderately or severely enlarged on the parasternal long- and short-axis views and from the apical 4-chamber, 2-chamber and long-axis views by 1 skilled ultrasonographer who was also blinded to the study. Outflow obstruction, valvular regurgitation, and systolic pulmonary artery pressures were quantified using Doppler echocardiographic techniques. Pulmonary regurgitation (PR) was graded as mild, moderate or severe based on the appearance of the regurgitant jet on color-flow Doppler imaging. Pulmonary stenosis (PS) was defined as above moderate when the Doppler-derived systolic pressure gradient across the pulmonary valve was ≥50 mmHg.

Statistical Analysis
Statistical significance was evaluated using paired and unpaired Student’s t-tests for comparisons between means. A chi-squared test and Fisher’s exact test were used for categorical data. All data are expressed as the mean ± standard deviation. Statistical significance was defined as a P-value < 0.05. The SPSS 11.0 software package (SPSS, Chicago, IL, USA) was used for statistical analysis.
Pregnancy Complicated With Repaired TOF

**Characteristics of Patients**

The 25 women with repaired TOF completed 40 pregnancies in our hospital from 1987 to April 2010. The number of deliveries complicated with repaired TOF showed a particular increase after the year 2000 (Figure 1); 21 patients were initially diagnosed with TOF, 3 with TOF and pulmonary atresia (PA), and 1 with TOF, PA and a major aortopulmonary collateral artery (MAPCA). One patient was complicated by hypertrophic cardiomyopathy. All patients underwent reparative surgery, including 7 who had a Blalock-Taussig shunt operation before TOF repair. The mean age at repair was 7.1 years (range: 1–36 years); 4 patients required reoperation: 2

**Table 1. Clinical Course of Obstetric Patients With Cardiac Events**

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>History of delivery</th>
<th>NYHA class</th>
<th>History of reoperation/arrhythmia/medication</th>
<th>Residual lesion</th>
<th>Pregnancy-associated events</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>34</td>
<td>0P</td>
<td>II–III VSD closure + TVR + PVR</td>
<td>Small VSD, Moderate TS</td>
<td>20W–PSVT ↑ antiarrhythmic agent</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PSVT p/o ABL</td>
<td></td>
<td>30W: complicated with PIH</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>β-blocker + diuretics for PSVT and HF</td>
<td></td>
<td>32W: bigeminal PVC with BP fall, right HF (severe TS) after CS</td>
</tr>
<tr>
<td>2</td>
<td>33</td>
<td>2P</td>
<td>I PSVT p/o ABL</td>
<td>Moderate PR</td>
<td>26W–NYHA II ↑ diuretics</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>28W–PSVT ↑, NSVT</td>
</tr>
<tr>
<td>3</td>
<td>28</td>
<td>1P</td>
<td>I None</td>
<td>Moderate PS, Moderate PR</td>
<td>33W–PSV severe</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>36W: excessive edema after delivery ⇒ diuretics</td>
</tr>
<tr>
<td>4</td>
<td>32</td>
<td>1P</td>
<td>I PMI for CAVB</td>
<td>Severe PR</td>
<td>34W–NYHA II, excessive edema ⇒ diuretics</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>35W: NSVT</td>
</tr>
<tr>
<td>5</td>
<td>35</td>
<td>1P</td>
<td>I LV-R communication closure</td>
<td>Moderate PR</td>
<td>9W–AT ↑ ⇒ β-blocker ↑,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>AFL/AT p/o ABL</td>
<td></td>
<td>13W–NYHA II, CTR ↑ ⇒ diuretics</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>la antiarrhythmic agent + verapamil + β-blocker for AT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>27</td>
<td>0P</td>
<td>II–III re-RVOTR β-blocker for AT, NSVT</td>
<td>Left PA obstruction</td>
<td>32W–NYHA II, CTR ↑, moderate TR</td>
</tr>
<tr>
<td>7</td>
<td>28</td>
<td>1P</td>
<td>I None</td>
<td>Moderate PR</td>
<td>34W: TR ↑, CVP ↑ after CS ⇒ diuretics</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>18W: rapid NSVT ⇒ β-blocker</td>
</tr>
</tbody>
</table>

NYHA, New York Heart Association; VSD, ventricular septal defect; TVR, tricuspid valve replacement; PVR, pulmonary valve replacement; PSVT, paroxysmal supraventricular tachycardia; p/o, post of; ABL, ablation; HF, heart failure; TS, tricuspid stenosis; PIH, pregnancy-induced hypertension; PVC, premature ventricular contraction; BP, blood pressure; CS, cesarian section; PR, pulmonary regurgitation; PMI, pacemaker implantation; CAVB, complete atioventricular block; LV-R, left ventricle-right atrium; AFL, atrial flutter; AT, atrial tachycardia; CTR, cardiothoracic ratio; RVOTR, right ventricle outflow reconstruction; PA, pulmonary artery; TR, tricuspid regurgitation; CVP, central venous pressure.

**Figure 2.** Flowchart of the obstetric patients in the study.
for right ventricular outflow tract reconstruction, 1 for patch closure for residual VSD and tricuspid valve replacement, and 1 for patch closure for LV-RA communication. Another patient underwent percutaneous transluminal angioplasty for left pulmonary artery stenosis twice before her pregnancy. Three patients had a pacemaker implanted for advanced atrioventricular block and another 3 had a history of catheter ablation for supraventricular tachycardia (SVT). Two patients had a residual VSD and 1 had left pulmonary artery occlusion. Moderate to severe PR was present in 15 patients, and moderate to severe PS was found in 2 patients. One patient had moderate tricuspid stenosis after tricuspid valve replacement.

With regard to NYHA class, 23 patients were in class I before pregnancy and 2 were in classes II–III. Four patients were prescribed medications before pregnancy; diuretics in 1 patient, an antiarrhythmia drug in 1, and both in 2. All 4 patients continued these medications during pregnancy. Two patients stopped taking angiotensin converting enzyme inhibitors before or immediately after pregnancy. Three patients had a smoking habit.

Pregnancy Course
The mean age at delivery was 29.1 years (range: 20–39 years); 14 patients had 1 delivery, 7 had 2 deliveries, and 4 had 3 deliveries. All pregnancies were singletons. All patients delivered successfully at a mean of 37.8 weeks of gestation (range: 30–41 weeks). There were 29 vaginal deliveries and 11 deliveries by CS. The reasons for CS were 1 case of maternal heart failure, 1 of PIH, 3 of fetal distress, 1 of arrest of labor, 3 of breech presentation, and 2 of repeated CS. Among the vaginal deliveries, 26 occurred under epidural anesthesia, and 1 and 2 antibiotics were used in 28 and 12 deliveries, respectively, for prophylaxis against endocarditis.

Cardiac Events
Cardiac events occurred in 7 of 40 deliveries (17.5%) in 7 patients (28%): 1 case of new onset of non-sustained ventricular tachycardia (NSVT) requiring treatment, 2 of heart failure, and 4 of worsening heart failure and arrhythmias including SVT and NSVT. Endocarditis and thromboembolic events did not occur. The clinical courses of patients complicated with cardiac events are shown in Table 1; 1 patient had TOF with PA and another had TOF with PA and MAPCA; 2 patients had cardiac events in the first pregnancy and none in later pregnancies, 4 had cardiac events in the second pregnancy, and 1 had a cardiac event in the third pregnancy (Figure 2).

Comparison of Patients With and Without Cardiac Events
A comparison of patients with and without pregnancy-associated cardiac events is shown in Table 2. A history of ablation for SVT and larger CTR within 1 year before pregnancy or during the first trimester were more frequent in patients with cardiac events. BNP levels (normal range <18.4 pg/ml) were higher in patients with cardiac events during pregnancy.
Figure 4. Changes in the echocardiographic parameters. The numbers on the horizontal axis are: (1) within 1 year before pregnancy to the first trimester, (2) in the second and third trimester (from 14 weeks of gestation to delivery), (3) after delivery to 1 month postpartum, (4) from 6 months to 1 year after delivery. LVDd, left ventricular end-diastolic diameter; LVDs, left ventricular end-systolic diameter; FS, fractional shortening; RVDd, right ventricular end-diastolic diameter.

Figure 5. Increased right heart dilation after each pregnancy.
measured during 15 pregnancies. Baseline BNP levels did not differ significantly between patients with and without cardiac events. However, peak BNP levels after second trimester were significantly higher in patients with cardiac events, with BNP >100 pg/ml in some of these patients (Figure 3).

Obstetric Events
Two patients were complicated with PIH: 1 had bigeminal premature ventricular contraction, and then BP fall after emergency CS because of PIH, and thus she was also included in the patients with cardiac events (Table 1, patient 1). There were 9 premature deliveries in 8 patients, because of maternal heart failure in 3 cases, premature rupture of membranes in 2, threatened premature labor in 3, and PIH in 1. Therefore, the mean weeks of delivery was shorter in patients with cardiac events than in those without cardiac events, but the difference was not significant. Of the 29 vaginal deliveries, 14 (48.2%) were complicated with postpartum hemorrhage. In contrast, none of the 11 CS deliveries resulted in postpartum hemorrhage. No patient needed a blood transfusion after delivery.

Offspring Events
There were no neonatal deaths. The mean birth weight was 2,665 g and was significantly lower for offspring of patients with cardiac events (Table 2). Two neonates (5.0%) were SGA, including 1 whose mother smoked during pregnancy and 1 whose mother took β-blockers for her history of NSVT. 2 had TOF, 1 had VSD, and 1 had atrial septal defect. Their 3 mothers had TOF without PA or right aortic arch. No patients were tested for genetic conditions.

Changes in Echocardiographic Parameters
Changes in the mean LVDd, LVDs, %FS, and RVdD during the perinatal period are shown in Figure 4. Mean RVdD was 26.7±6.9 mm within 1 year before pregnancy to the first trimester, 27.7±9.9 mm in the second and third trimester, 28.2±10.1 mm after delivery to 1 month postpartum, and 29.6±10.2 mm at 6 months to 1 year after delivery. RVdD at 6 months to 1 year after delivery became significantly greater than that within 1 year before pregnancy to the first trimester. Right ventricular size was able to graded retrospectively in 24 pregnancies and the changes after each pregnancy are shown in Figure 5. Right heart dilatation tended not to recover after pregnancy and to progress with each pregnancy.

Discussion
Our data suggest that most pregnancies in patients with repaired TOF have a favorable outcome, which is compatible with previous reports. Rates of 7–12% have been reported for maternal cardiac events during pregnancy after repaired TOF,12,18,12 and the rate in this study was 17.5%. The reasons of our higher rate of maternal cardiac events may be (1) inclusion of patients with PA and/or MAPCA in the study and (2) the hospital is a referral hospital. Left ventricular dysfunction, severe pulmonary hypertension, decreased subpulmonary ventricular ejection fraction and/or severe PR,4 use of cardiac medication pre-pregnancy, history of arrhythmia, and prior pulmonary valve replacement10 have been proposed as predictors of maternal cardiac events during pregnancy. In our study, the predictors of maternal cardiac events were a history of ablation for SVT and large CTR on chest radiograph. This is the first report to show the potential value of chest radiography for predicting maternal cardiac events. Because the number of patients was small, NYHA class ≥II, history of reoperation, use of medication pre-pregnancy, and wider QRS duration on ECG did not reach a significant level as risk factors for cardiac events, we were unable to perform a multivariate analysis of pregnancy-associated risk factors. Moreover, RV dilatation, RVdD, and over-moderate PR on echocardiography were not significantly different between patients with and without cardiac events, whereas CTR reflecting an enlarged right heart was significantly different. We have to consider that the efficacy of echocardiography was not adequate to assess the right heart. A further study is required to investigate these factors.

Management of patients late after repair of TOF has recently focused on the risk of arrhythmia and sudden cardiac death.13 A Japanese multicenter study of the incidence, manifestation and management of arrhythmia in congenital heart disease during pregnancy found that SVT tended to require antiarrhythmic agents more frequently than ventricular arrhythmia.14 The current study results clearly show the importance of a prior history of SVT in the evaluation of the risk of pregnancy. PR and progressive dilation of the RV are closely related to SVT and sudden death.15 Moreover, heart rate variability, which is a significant marker of autonomic nervous function and may predict tachyarrhythmia, may be significantly impaired in pregnant women after repair of congenital heart disease.16 An arrhythmogenic effect could cause significant hemodynamic compromise in both the mother and fetus in women with repaired TOF with subclinical LV intolerance and RV dilatation during pregnancy.17,18 Therefore, arrhythmia and an enlarged RV should be viewed with particular caution in the pregnancy management of these women.

BNP is useful biomarker for the assessment of congestive heart failure in congenital heart disease, as well as other heart diseases.19 Tanous et al measured the BNP levels in 66 women with heart disease and found that those with events during pregnancy (n=8) had BNP >100 pg/ml, whereas no women with BNP ≤100 pg/ml had adverse events (negative predictive value: 100%).20 In our study, in which we followed BNP levels in 15 patients, several of those with cardiac events showed a peak BNP level ≤100 pg/ml. BNP levels at baseline did not predict cardiac events, and the timing of the examination of BNP level after second trimester was similar to the timing for the manifestation of heart failure. Thus, we consider BNP levels not as a predictor of heart failure, but as a useful marker to identify and to manage these obstetric patients.

Ventricular size and function assessed by cardiac magnetic resonance imaging (MRI) are good predictors for major adverse clinical outcomes in patients late after repair of TOF.21 Because the current study showed that RVdD on routine echocardiographic examination was not an excellent predictor of cardiac events, MRI may be more applicable for screening to assess the risk of pregnancy in severely affected patients.

Japanese guidelines for the indication and management of pregnancy and delivery in women with heart disease recommend the use of antibiotic prophylaxis at the time of delivery for patients with repaired cyanotic heart diseases, including TOF. All patients in our study received antibiotic prophylaxis against endocarditis, and there was no occurrence of endocarditis. The incidence of PIH was 5%, which is similar to that in the Japanese general population (4%).22 Because one of the patients with PIH had a BP fall from a bigeminal pulse, obstetric events such as PIH may cause fetomaternal morbidity in patients with repaired TOF to a greater extent than in the general population.

In our study population, postpartum hemorrhage occurred in approximately half of the women after vaginal delivery, which is a much higher rate than the 8.8% in a previous report.23
Asian race, antenatal hospitalization, induction of labor, and epidural anesthesia have been suggested as risk factors for postpartum hemorrhage after vaginal delivery. Because many of the patients were delivered by induction under epidural anesthesia, the rate of postpartum hemorrhage might have been increased. Careful management of atonic bleeding is required, especially after vaginal delivery in patients with repaired TOF.

The risk of recurrence of congenital heart disease in women with repaired TOF has been reported to range from 0% to 9.8%. The recurrence rate in our patients was approximately 10%, which is close to the rate of 9.8% in the study by Pedersen et al, in which it was also pointed out that the rate of congenital cardiac disease in the offspring is 4.8%, excluding siblings with chromosome 22q11.2 deletion syndrome.

We did not perform genetic tests in our patients and it is possible that some of the patients had a genetic condition. However, all 3 mothers whose children showed congenital heart disease in this study were not TOF with PA and right aortic arch, which suggests the incidence of chromosome 22q11.2 deletion syndrome.

Regarding cardiac size, Uebing et al reported that pregnancy itself was associated with a persistent increase in subpulmonary ventricular size in patients with repaired TOF using an analysis that did not take the number of deliveries into consideration. Our data suggest that the right heart tends to be more and more dilated after the second and third deliveries, which indicates that pregnancy can affect long-term prognosis in patients with repaired TOF. Clarification of the long-term effects of pregnancy in these patients requires a long-term observational study to compare patients with and without a history of pregnancy. In general, the number of pregnancies complicated with repaired TOF is increasing and further studies are required to establish better management to minimize the risk of pregnancy and give a better long-term prognosis.

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Disclosures

None.

References