ORIGINAL RESEARCH

Pregnancy Outcomes in Women After Arterial Switch Operation for Transposition of the Great Arteries: Results From ROPAC (Registry of Pregnancy and Cardiac Disease) of the European Society of Cardiology EURObservational Research Programme

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BACKGROUND: In the past 3 decades, the arterial switch procedure has replaced the atrial switch procedure as treatment of choice for transposition of the great arteries. Although survival is superior after the arterial switch procedure, data on pregnancy outcomes are scarce and transposition of the great arteries after arterial switch is not yet included in the modified World Health Organization classification of maternal cardiovascular risk.

METHODS AND RESULTS: The ROPAC (Registry of Pregnancy and Cardiac disease) is an international prospective registry of pregnant women with cardiac disease, part of the European Society of Cardiology EURObservational Research Programme. Pregnancy outcomes in all women after an arterial switch procedure for transposition of the great arteries are described. The primary end point was a major adverse cardiovascular event, defined as combined end point of maternal death, supraventricular or ventricular arrhythmias requiring treatment, heart failure, aortic dissection, endocarditis, ischemic coronary events, and thromboembolic events. Altogether, 41 pregnant women (mean age, 26.7±3.9 years) were included, and there was no maternal mortality. A major adverse cardiovascular event occurred in 2 women (4.9%): heart failure in one (2.4%) and ventricular tachycardia in another (2.4%). One woman experienced fetal loss, whereas no neonatal mortality was observed.

CONCLUSIONS: Women after an arterial switch procedure for transposition of the great arteries tolerate pregnancy well, with a favorable maternal and fetal outcome. During counseling, most women should be reassured that the risk of pregnancy is low. Classification as modified World Health Organization risk class II seems appropriate.

Key Words: arterial switch operation ■ pregnancy and cardiac disease ■ pregnancy outcomes ■ transposition of the great arteries
Tutarel et al Pregnancy After Arterial Switch for TGA

The first successful arterial switch procedure for patients with transposition of the great arteries (TGA) was reported in 1975 by Jatene and colleagues.1 It establishes a biventricular circulation, where the morphologic left ventricle supports the systemic circulation. This is in contrast to the previously performed atrial switch procedure, after which the morphologic right ventricle acts as a systemic ventricle. This systemic right ventricle is prone to fail, leading to heart failure and a diminished survival rate.2 Therefore, for the past 30 years, the arterial switch has been the surgical approach of choice for TGA.3 Consequently, the number of women after an arterial switch procedure for TGA reaching childbearing age is increasing, although not without complications. Neoaoetric valve regurgitation, dilatation of the aortic root, ischemia attributable to coronary reinsertion problems, ventricular dysfunction, and right ventricular outflow tract obstruction have all been reported after the arterial switch.4 Because pregnancy poses a hemodynamic challenge to the maternal circulation, it might increase the risk for these complications. Data on the outcome of pregnancies in women after an arterial switch procedure are scarce. Single cases of successful pregnancies were reported in 2001 and 2006,5,6 as well as retrospective series from single centers7–9 and one study from 2 centers.3 These reported the outcome of pregnancies in 9, 10, 11, and 15 women, respectively. The rate of adverse events differed significantly between these reports, whereas larger prospective studies are lacking, meaning that uncertainty remains about the impact of pregnancy in women after an arterial switch procedure.3,7–9 According to the modified World Health Organization classification, the most commonly used disease-specific risk assessment of pregnancy in women with cardiac disease.10 Consequently, the aim of this study is to provide a much more accurate assessment of maternal and fetal outcomes of pregnancy in this group of women.

METHODS

Study Design

The ROPAC (Registry of Pregnancy and Cardiac disease) is an international, prospective, observational registry of pregnant patients with structural heart disease, including valvular and congenital heart disease, ischemic heart disease, aortic pathological features, and pulmonary arterial hypertension. Study design and methods have been described previously.11 The European Society of Cardiology working groups on congenital heart disease and valvular heart disease initiated ROPAC in 2007 and subsequently it was embedded in the ERObservational Research Programme of the European Society of Cardiology.

Ethical approval or Institutional Review Board approval as well as patients’ informed consent were obtained if necessary, according to local requirements.

Pregnant women who were included in the ROPAC prospectively between January 2007 and January 2018 and had previously undergone an arterial switch procedure for TGA were included in this study. The data that support the findings of this study are available from the corresponding author on reasonable request.

Data

The ROPAC study protocol and the first results of this registry were published in 2013.11 Patients with a diagnosis of TGA treated with an arterial switch procedure were identified from the registry and compared with the rest of the total ROPAC cohort. Baseline characteristics collected before pregnancy

Nonstandard Abbreviations and Acronyms

ROPAC Registry of Pregnancy and Cardiac disease
TGA transposition of the great arteries

CLINICAL PERSPECTIVE

What Is New?

• Women after arterial switch operation for transposition of the great arteries tolerate pregnancy well, on the basis of 41 pregnancies in a prospective worldwide registry.
• In this cohort, there was no maternal mortality, and major adverse cardiovascular events occurred in 4.9%, as heart failure (2.4%) and ventricular tachycardia (2.4%).
• Prematurity (17.1%) was the most important fetal complication, followed by low birth weight (14.6%), but fetal loss occurred in only 2.4%.

What Are the Clinical Implications?

• Women after arterial switch for transposition of the great arteries can be counseled that pregnancy is safe, with a low risk of cardiac complications.
• Currently unclassified in the modified World Health Organization classification for maternal cardiovascular risk, this study suggests that pregnancy after arterial switch for transposition of the great arteries can be classified as modified World Health Organization risk class II.
Definitions and End Points
The primary combined end point was the occurrence of a major adverse cardiovascular event, defined as combined end point of maternal death, supraventricular or ventricular arrhythmias requiring treatment, heart failure, aortic dissection, endocarditis, ischemic coronary event, and other thromboembolic events. The secondary end points were adverse obstetric outcomes and adverse fetal/neonatal outcomes. Heart failure was defined according to the American College of Cardiology/American Heart Association guidelines,13 and heart failure episodes were only included when they required hospital admission, new treatment, or change in the existing treatment regimen. Ventricular function was categorized as normal, mildly impaired, moderately impaired, or severely impaired. Postpartum hemorrhage was defined as increased blood loss during delivery up to 24 hours postpartum, requiring specific interventions. Hemolysis, elevated liver enzymes, low platelets syndrome, preeclampsia and eclampsia, and pregnancy-induced hypertension were defined according to the International Society for the Study of Hypertension in Pregnancy 2018 statement.14 Fetal mortality was defined as the death of a fetus after 20 weeks of gestation until birth. Neonatal mortality was defined as the death of a live-born baby in the first 6 months of life. Premature birth was defined as birth before 37 weeks of gestation. Low birth weight was defined as a birth weight of <2500 g. Low Apgar score was defined as an Apgar score at 5 minutes of <7. All outcomes were examined for the duration of the pregnancy and up to 6 months postpartum.

Statistical Analysis
Data are presented as mean values with SD if normally distributed and median with interquartile range if skewed. Categorical data are presented as frequencies and percentages. Baseline characteristics and outcomes were compared between women after arterial switch for TGA and the other pregnancies in the ROPAC cohort, using Student t tests and χ² tests where appropriate. P<0.05 (2-sided test) was considered significant. All statistical tests and analyses were performed with SPSS version 21.0 (SPSS Inc, Chicago, IL).

RESULTS
There were 41 women after arterial switch for TGA among the 5739 patients included in ROPAC from January 2007 to January 2018.15 Baseline characteristics are presented in Table 1. Their mean age was 26.7±3.9 years, 21 women (51.2%) were primigravida, and 2 women (4.9%) were from an emerging country, as opposed to 40% in the rest of the ROPAC cohort (P<0.001). Most of the women (97.6%) were asymptomatic or had only mild symptoms (New York Heart Association class I/II) before pregnancy. Only one woman was in New York Heart Association class III. Cardiac medication was used by 24.4% before pregnancy.

Maternal Outcomes
Maternal cardiac outcomes of pregnancy are presented in Table 2. There was no maternal mortality either in pregnancy or up to 6 months after delivery, whereas it occurred in 0.7% of the other ROPAC pregnancies (0% versus 0.7%; P=0.560). Hospital admission for a cardiac reason was required in one woman (2.4%) because of heart failure. The woman had a history of a Blalock-Taussig shunt before the arterial switch procedure and had experienced heart failure symptoms before pregnancy. Unfortunately, a prepregnancy echocardiogram was not available. She was delivered at 36 weeks gestation by an elective cesarean section. In the third month postpartum, acute heart failure developed. At that point, left ventricular systolic function was moderately impaired, with an ejection fraction of 45%, without significant aortic or pulmonary valve dysfunction.

There were no cases of supraventricular tachycardia, and ventricular tachycardia occurred in one woman (2.4%). In the rest of the ROPAC cohort, ventricular tachycardia occurred in 1.6% (2.4% versus 1.6%; P=0.652), whereas supraventricular tachycardia occurred in 1.7% (0% versus 1.7%; P=0.404). Before her arterial switch procedure, this woman underwent banding of the pulmonary artery and a Blalock-Taussig shunt. Before pregnancy, echocardiography showed good biventricular function without significant valve dysfunction. During the second and third trimesters, ventricular tachycardia and frequent ventricular ectopic beats occurred, which were effectively treated with metoprolol without requiring hospital admission. After induction of labor at 38 weeks of gestation, she had a vacuum-assisted vaginal delivery. After pregnancy, no further arrhythmias were noted.
### Table 1. Baseline Characteristics

| Characteristic                                                                 | TGA After Arterial Switch (n=41) | Other ROPAC (n=5698) | P Value |
|-------------------------------------------------------------------------------|----------------------------------|----------------------|---------|
| **Age, mean (SD), y**                                                        | 26.7 (3.9)                       | 29.8 (5.6)           | 0.002   |
| **Living in an emerging country**                                            | 2 (4.9)                          | 2279 (40)            | <0.001  |
| **Primigravida**                                                              | 21 (51.2)                        | 2552 (44.9)          | 0.420   |
| **Current smoking**                                                           | 1 (2.4)                          | 227 (4.6)            | 0.617   |
| **Associated cardiac defects**                                               |                                  |                      |         |
| Ventricular septal defect                                                    | 13 (31.7)                        | 703 (12.3)           | <0.001  |
| PDA                                                                           | 4 (9.8)                          | 145 (2.5)            | 0.004   |
| Coarctation of the aorta                                                    | 2 (4.9)                          | 301 (5.3)            | 0.129   |
| **Prior interventions/surgery**                                              |                                  |                      |         |
| Arterial switch                                                              | 41 (100)                         | 41 (0.7)             | NA      |
| Time since arterial switch, mean (SD), y                                     | 25.7 (0.7)                       | NA                   | NA      |
| Ventricular septal defect closure                                            | 13 (31.7)                        | 908 (15.9)           | 0.006   |
| Pulmonary banding                                                            | 12 (29.3)                        | NA                   | NA      |
| Rashkind procedure/surgical atrial septostomy                                | 9 (22.0)                         | NA                   | NA      |
| Blalock-Taussig shunt                                                        | 5 (12.2)                         | NA                   | NA      |
| Pulmonary valve intervention*                                                | 4 (9.8)                          | 230 (4)              | 0.065   |
| Coarctation of aorta resection                                               | 2 (4.9)                          | 272 (4.8)            | 0.150   |
| Percutaneous coronary intervention                                           | 1 (2.4)                          | 63 (1.1)             | 0.418   |
| Aortic surgery                                                               | 1 (2.4)                          | 235 (4.1)            | 0.588   |
| Dilatation of pulmonary artery stenosis                                      | 1 (2.4)                          | NA                   | NA      |
| PDA closure                                                                  | 1 (2.4)                          | NA                   | NA      |
| **Prepregnancy cardiac status**                                              |                                  |                      |         |
| Diabetes mellitus                                                            | 0 (0)                            | 90 (2)               | 0.412   |
| Chronic hypertension                                                         | 1 (2.4)                          | 379 (6.8)            | 0.271   |
| Signs of heart failure                                                       | 1 (2.4)                          | 595 (10.6)           | 0.090   |
| Left ventricular ejection fraction <40%                                       | 1 (2.4)                          | 252 (4.4)            | 0.538   |
| Pulmonary hypertension                                                       | 1 (2.4)                          | 44 (0.8)             | 0.568   |
| NYHA class                                                                   |                                  |                      |         |
| I                                                                             | 38 (92.7)                        | 4169 (73.2)          | 0.005   |
| II                                                                            | 2 (4.9)                          | 1189 (20.9)          | 0.012   |
| III                                                                           | 1 (2.4)                          | 175 (3.1)            | 0.815   |
| IV                                                                            | 0 (0)                            | 28 (0.5)             | 0.653   |
| Aortic stenosis                                                              | 0 (0)                            | 397 (7)              | 0.077   |
| Aortic regurgitation                                                         | 14 (34.1)                        | 876 (15.4)           | <0.001  |
| Mild                                                                          | 13 (31.7)                        | 585 (10.4)           | 0.012   |
| Moderate                                                                     | 1 (2.4)                          | 236 (4.2)            | 0.001   |
| Severe                                                                        | 0 (0)                            | 55 (1)               |         |
| Pulmonary stenosis                                                           | 14 (34.1)                        | 443 (8)              | <0.001  |
| Aortic dilatation                                                            | 4 (9.8)                          | 170 (3)              | 0.012   |
| **Prepregnancy cardiac medication**                                          | 10 (24.4)                        | 2059 (36.1)          | 0.119   |
| **β Blockers**                                                               | 2 (4.9)                          | 561 (9.8)            | 0.287   |
| **Diuretics**                                                                | 1 (2.4)                          | 216 (3.8)            | 0.651   |
| **ACE inhibitor**                                                            | 2 (4.9)                          | 155 (2.7)            | 0.399   |
| **Antiplatelet drugs**                                                       | 2 (4.9)                          | 232 (4.1)            | 0.795   |
| **Drug name not included in database**                                       | 3 (7.3)                          | NA                   | NA      |

Values are number (percentage) if not otherwise stated. ACE indicates angiotensin-converting enzyme; NA, not available; NYHA, New York Heart Association; PDA, persistent ductus arteriosus; ROPAC, Registry of Pregnancy and Cardiac disease; and TGA, transposition of the great arteries.

*All valve interventions were surgical repairs of the pulmonary valve; there were no aortic valve interventions or any valve replacements.*
On the basis of these 2 events, the total major adverse cardiovascular event rate was 4.9%, and no other events or interventions occurred during pregnancy or in the 6-month follow-up after delivery. An echocardiographic assessment of ventricular systolic function before pregnancy or during the first trimester was available in 23 women (56.1%). Left ventricular systolic function was normal in 22 (95.7%), whereas it was moderately impaired in 1 (4.3%). Right ventricular systolic function was normal in 18 women (78.3%) and moderately impaired in 5 (21.7%). Serial data (prepregnancy and postpartum) were available in 13 women (Figure 1). No deterioration in ventricular function or aortic valve function was observed.

**Obstetric and Fetal Outcomes**

Obstetric and fetal outcomes are presented in Table 3. Hypertensive disorders of pregnancy occurred in 2 pregnancies (4.9%), compared with 4.4% of the rest of the ROPAC cohort (P=0.865). Median gestational age at delivery was 39 weeks (interquartile range, 37–40 weeks), and mean birth weight was 2962.2±99.8 g, with low birth weight in 14.6% versus 11.7% (P=0.561) in the other ROPAC pregnancies. There were 7 premature births (17.1%) at a median gestational age of 35 weeks (interquartile range, 34–36 weeks), of which 5 were spontaneous labors and 2 were medically induced for obstetric reasons. A cesarean section was performed in 46.3% of women after arterial switch for TGA, compared with 49.8% of the rest of the ROPAC cohort (P=0.662). Fetal death occurred once in our cohort (2.4%), and in 1.3% of the other women included in ROPAC (P=0.778).

**DISCUSSION**

The ROPAC, an international prospective registry, studies the outcomes of pregnancy in women with structural heart disease. In this article, we have focused on women with TGA treated with an arterial switch procedure, and our findings are summarized in Figure 2. Nearly all women tolerated pregnancy well, with a low rate of major adverse cardiovascular events (only 4.9%) and without maternal or neonatal mortality. Fetal mortality occurred in only one pregnancy, whereas in terms of maternal morbidity, heart failure and arrhythmias both also occurred only once.

### Maternal Outcomes

This first large prospective study shows that maternal outcome is favorable, whereas by comparison in previous retrospective studies, maternal cardiac events occurred in 12% to 29% of women,3,8,9 although one recent study (n=15) reported no cardiac events at all.7 Arrhythmias and heart failure were most frequently encountered in these older studies (Figure 3). The wide variation in the number of events is probably because of the small number of women included in these studies. Furthermore, some of these reports included women from an earlier surgical era and with a more severe prior clinical course.3,7 Indeed, both women with cardiac events in our study had had a Blalock-Taussig shunt before the arterial switch procedure, probably illustrating their more complex clinical course.

Our contemporary prospective data are reassuring about maternal complications. This information is critically important for women with an arterial switch who are contemplating pregnancy, as they can now be reassured that their chance of complications is low. Because of the low number of events, an analysis to identify risk factors for adverse outcomes was not possible.

Most patients in our study had a normal left (95.7%) and right (78.3%) ventricular systolic function prepregnancy. Furthermore, in the women with serial echocardiographic data, there was no deterioration in left or right ventricular function (Figure 1). In the study of Horiuchi and colleagues, 50% of women with a cardiac event during pregnancy and 20% of those without a cardiac event had

| Table 2: Maternal Outcomes of Pregnancy |
|----------------------------------------|
| **Outcome**                          | **TGA After Arterial Switch (n=41)** | **Other ROPAC (n=5698)** | **P Value** |
|----------------------------------------|
| Maternal mortality ≤6 mo postpartum    | 0 (0)                                  | 40 (0.7)                 | 0.590       |
| Hospital admission for a cardiac reason| 1 (2.4)                                 | 757 (13.3)               | 0.041       |
| Heart failure                         | 1 (2.4)                                 | 654 (11.5)               | 0.070       |
| Supraventricular tachycardia          | 0 (0)                                  | 95 (1.7)                 | 0.404       |
| Ventricular tachycardia               | 1 (2.4)                                 | 89 (1.6)                 | 0.652       |
| Thromboembolic events                 | 0 (0)                                  | 87 (1.5)                 | 0.425       |
| Endocarditis                          | 0 (0)                                  | 33 (0.6)                 | 0.625       |
| Acute coronary syndrome               | 0 (0)                                  | 24 (0.4)                 | 0.677       |
| Aortic dissection                     | 0 (0)                                  | 5 (0.1)                  | 0.849       |

Values are number (percentage). ROPAC indicates Registry of Pregnancy and Cardiac disease; and TGA, transposition of the great arteries.
a reduced left ventricular function. This might explain the higher number of cardiac events in their study. During follow-up, no further deterioration of left ventricular function was observed. Similar to our experience, Stoll and colleagues reported no adverse cardiac events, with all women having normal left ventricular systolic function before their first pregnancy, whereas one woman had a mildly impaired function after her second pregnancy. Therefore, an echocardiogram before pregnancy is an important tool for risk assessment.

**Table 3. Obstetric and Fetal Outcomes of Pregnancy**

| Outcome                                                   | TGA After Arterial Switch (n=41) | Other ROPAC (n=5698) | P Value |
|-----------------------------------------------------------|----------------------------------|----------------------|---------|
| Pregnancy-induced hypertension                           | 0 (0)                            | 77 (1.4)             | 0.454   |
| (Pre) eclampsia or HELLP syndrome                        | 2 (4.9)                          | 170 (3)              | 0.478   |
| Gestational diabetes mellitus                            | 0 (0)                            | 160 (2.8)            | 0.274   |
| Postpartum hemorrhage                                     | 2 (4.9)                          | 168 (2.9)            | 0.468   |
| Cesarean section                                          | 19 (46.3)                        | 2662 (49.8)          | 0.662   |
| Emergency cesarean section                               | 6 (14.6)                         | 760 (13.3)           | 0.808   |
| Emergency cesarean section for cardiac reason            | 0 (0)                            | 132 (2.3)            | 0.324   |
| Fetal death                                               | 1 (2.4)                          | 71 (1.2)             | 0.778   |
| Neonatal death                                            | 0 (0)                            | 33 (0.6)             | 0.625   |
| Fetal congenital heart disease                            | 0 (0)                            | 156 (2.7)            | 0.283   |
| Premature birth                                           | 7 (17.1)                         | 898 (18)             | 0.947   |
| IUGR                                                      | 1 (2.4)                          | 253 (4.4)            | 0.535   |
| Low Apgar scores                                          | 2 (4.9)                          | 395 (6.9)            | 0.606   |
| Low birth weight                                          | 6 (14.6)                         | 667 (11.7)           | 0.561   |
| Birth weight, mean (SD), g                               | 2962.2 (99.8)                    | 2970.9 (639.6)       | 0.941   |

Values are number (percentage), except for birth weight. HELLP indicates hemolysis, elevated liver enzymes, low platelet count; IUGR, intrauterine growth retardation; ROPAC, Registry of Pregnancy and Cardiac disease; and TGA, transposition of the great arteries.
In comparison to previous reports of pregnancy after the atrial switch procedure, which reported several complications, most frequently arrhythmias and heart failure, with a rate between 7% and 22% and between 7% and 21%, respectively, depending on the study design and patient population, the maternal outcome in our cohort after the arterial switch procedure is much more favorable. These results emphasize the advantages of the later procedure further.

**Obstetric and Fetal Outcomes**

In our contemporary cohort, both obstetric and fetal complications were less frequent than reported by previous studies. Interestingly, the most recent...
study reported an unexpected high incidence of maternal obstetric complications (58.8%). Most of these complications were attributable to postpartum hemorrhage, whereas this occurred in only 4.9% of women in our cohort. Maternal obstetric complications are not mentioned in detail in the other 2 series.3,7

The most frequent observed fetal complication in our study was premature birth (17.1%), followed by low birth weight (14.6%). Both are not significantly different from the rest of the ROPAC cohort. Iatrogenic premature birth was because of obstetric reasons and never because of cardiac causes. Although one fetal loss was observed, there was no neonatal mortality. Unfortunately, not all previous studies commented on the fetal outcome in detail. Stoll and colleagues reported premature birth in 9.1% of pregnancies,7 whereas in the series of Horiuchi and colleagues, 21% of pregnancies did not reach full term.8 In the latter study, low birth weight was observed in 27%,8 whereas Tobler et al reported a lower rate, with 14.3%.3 Therefore, the results of our study provide reassurance about the fetal outcome compared with previous literature.

A cesarean section was performed in 46.3% of women in our study, which is comparable to the high number of women with a cesarean section in the whole ROPAC cohort (49.8%; P=0.662). In the previous studies, the frequency of cesarean sections varied between 36% and 47%.7–9 These high rates could be attributable to the congenital heart defect of the mother, because it is conceivable that women with heart disease in general are handled with more care and apprehension by treating physicians and are thus given a cesarean section (as many physicians prefer this apparently more controlled environment). This could be especially true for congenital heart defects, for which data on pregnancy outcomes are scarce as they are for patients with an arterial switch procedure for TGA. However, the available data do not support this approach,10 and guidelines recommend that a cesarean section should only be considered for obstetric indications or a limited number of cardiac indications, including labor on oral anticoagulants, aggressive aortic pathological features, acute intractable heart failure, and severe pulmonary hypertension.10 This is also reflected by the reassuringly low number (15%) of emergency cesarean sections in our study, none of which was attributable to cardiac reasons, which confirms the results of Stoll et al,7 whereas it is much lower than the recently reported 63%.9 The last report had an unexpectedly high number of obstetric complications. In addition, the use of Cesarean section as a primary mode of delivery is country and center dependent and so could influence the numbers in our multicenter study.

Interestingly, only 4.9% of women from our cohort are living in an emerging country, as opposed to 40% of the rest of the ROPAC cohort (P<0.001). The main reason for this finding could be that the arterial switch procedure for TGA was often not available to children born in the developing world for a long period.21 In recent years, this has changed,22 and therefore, we can expect an increase in the numbers of women after an arterial switch procedure for TGA reaching childbearing age in these emerging countries.

A limitation of our study is that serial echocardiographic data were available in only a limited number of women. Therefore, analysis on the course and outcome of ventricular function as well as aortic and pulmonary valve function, especially considering the neo-aortic valve, was not possible in all women. Despite these limitations, this prospective registry included the largest number of women after an arterial switch procedure for TGA reported to date, providing important information related to the maternal and fetal outcome in these women.

CONCLUSIONS

In conclusion, women after an arterial switch procedure for TGA tolerate pregnancy well, with a favorable maternal and fetal outcome. Therefore, women after an arterial switch procedure for TGA should be counseled that pregnancy is low risk. With a major adverse cardiac event rate of 4.9%, this corresponds to risk class modified World Health Organization II.

APPENDIX

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