Circulation

ORIGINAL RESEARCH ARTICLE

Pregnancy Outcomes in Women With Rheumatic Mitral Valve Disease

Results From the Registry of Pregnancy and Cardiac Disease

Editorial, see p 817

Iris M. van Hagen, MD, PhD
Sara A. Thorne, MD
Nasser Taha, MD
Ghada Youssef, MD
Amro Elnagar, MD
Harald Gabriel, MD
Yahia ElRakshy, MD
Bernard Iung, MD
Mark R. Johnson, MD, PhD
Roger Hall, MD
Jolien W. Roos-Hesselink, MD, PhD
On behalf of the ROPAC Investigators and EORP Team

BACKGROUND: Cardiac disease is 1 of the major causes of maternal mortality. We studied pregnancy outcomes in women with rheumatic mitral valve disease.

METHODS: The Registry of Pregnancy and Cardiac Disease is an international prospective registry, and consecutive pregnant women with cardiac disease were included. Pregnancy outcomes in all women with rheumatic mitral valve disease and no prepregnancy valve replacement is described in the present study (n=390). A maternal cardiac event was defined as cardiac death, arrhythmia requiring treatment, heart failure, thromboembolic event, aortic dissection, endocarditis, acute coronary syndrome, and hospitalization for other cardiac reasons or cardiac intervention. Associations between patient characteristics and cardiac outcomes were checked in a 3-level model (patient–center–country).

RESULTS: Most patients came from emerging countries (75%). Mitral stenosis (MS) with or without mitral regurgitation (MR) was present in 273 women, isolated MR in 117. The degree of MS was mild in 20.9%, moderate in 39.2%, severe in 19.8%, and severity not classified in the remainder. Maternal death during pregnancy occurred in 1 patient with severe MS. Hospital admission occurred in 23.1% of the women with MS, and the main reason was heart failure (mild MS 15.8%, moderate 23.4%, severe 48.1%; $P<0.001$). Heart failure occurred in 23.1% of patients with moderate or severe MR. An intervention during pregnancy was performed in 16 patients, 14 had percutaneous balloon mitral commissurotomy, and 2 had surgical valve replacement (1 for MS, 1 for MR). In multivariable modeling, prepregnancy New York Heart Association class >1 was an independent predictor of maternal cardiac events. Follow-up at 6 months postpartum was available for 53%, and 3 more patients died (1 with severe MS, 1 with moderate MS, 1 with moderate to severe MR).

CONCLUSIONS: Although mortality was only 1.9% during pregnancy, ≈50% of the patients with severe rheumatic MS and 23% of those with significant MR developed heart failure during pregnancy. Prepregnancy counseling and considering mitral valve interventions in selected patients are important to prevent these complications.

Key Words: pregnancy ■ rheumatic heart disease ■ valvular heart disease ■ women ■ women and minorities

Sources of Funding, see page 815

http://circ.ahajournals.org

Clinical Perspective

What Is New?

- This international prospective registry including women with rheumatic mitral valve disease shows that women with mild and asymptomatic rheumatic mitral valve disease tolerate pregnancy well, but that morbidity is especially high in women with severe mitral valve stenosis.
- Women with moderate, severe, or symptomatic rheumatic mitral valve disease are at high to very high risk of heart failure during pregnancy.

What Are the Clinical Implications?

- Given the high rate of complications during pregnancy, a percutaneous balloon mitral commissurotomy, which has a low risk, may be a feasible treatment for young women with moderate or severe mitral stenosis who have a desire for pregnancy, even if they are asymptomatic.
- Adequate counseling of adolescents and young women with rheumatic mitral valve disease about the risks of pregnancy is of utmost importance to convince them to see a cardiologist before getting pregnant. Implementation of current guidelines in clinical practice is clearly needed.

Rheumatic heart disease is a major problem, with ≤1.4 million people dying each year, and is a leading disease in the young, especially in emerging countries. In more developed economies, the diagnosis of rheumatic heart disease is rare and typically found in recent immigrants.[1–3] It poses a particular problem in pregnant women, in whom the diagnosis is often delayed or missed. In emerging countries, rheumatic valve disease is the most common cardiac disease in pregnant women and the most important cause of maternal death.[4–7] Mitral valve stenosis in particular is a high-risk condition.[8]

Maternal mortality in general has decreased in the past decade, but over the same period, cardiac maternal death has not declined.[9,10] Large prospective studies in pregnant women with heart disease in general and specifically in women with rheumatic heart disease are lacking. Such studies are needed to provide evidence for guidelines on the management of pregnancy in women with heart disease[11,12] and to counsel women with rheumatic heart disease who are contemplating a pregnancy. Further, contemporary data on the outcomes of pregnancy in women with rheumatic mitral valve disease will help to stratify risk, enabling high-risk women to be identified and appropriately counseled and managed. The aim of this study is to assess maternal and fetal outcomes of pregnancy in women with rheumatic mitral valve disease.

METHODS

The ROPAC (Registry of Pregnancy and Cardiac Disease) is an international prospective and ongoing registry that was established to study a large number of pregnant women with structural heart disease. ROPAC was initiated by the European Society of Cardiology (ESC) working groups on congenital heart disease and valvular heart disease in 2007 and embedded in the EORP (Eurobservational Research Programma) of the ESC. The data, analytic methods, and study materials will be available on request to other researchers for purposes of reproducing the results or replicating the procedure. When required, ethical approval or Institutional Review Board approval was obtained (eg, in Germany, United States, Canada, and Belgium). However, in some countries, the procedure to obtain ethical approval was waived because of the anonymized and untraceable nature of the data. Informed consent was obtained from patients if required by the local independent review board.

Prospective data collection started in January 2008, and for the current study we included data from patients with a term date up to October 2013 and follow-up up to April 2014. An extensive description of the study protocol and methods has been published previously.[4] Participating centers included all consecutive pregnant patients with heart disease. For this analysis, the outcomes of pregnancy for all patients with rheumatic mitral valve disease in ROPAC was analyzed. Women with a mechanical or bioprosthetic valve have already been described elsewhere and were excluded from the current study.[13]

Data Collection

Prepregnancy patient characteristics that were collected included age, parity, cardiac diagnosis, previous interventions, medication, smoking, diabetes mellitus, hypertension, obstetric history, and, if available, echocardiographic parameters. Countries were defined as emerging or advanced according to the International Monetary Fund.[14] Participating centers and countries can be found in a previous publication,[4] and countries that included women with rheumatic mitral valve disease are also listed in the online-only Data Supplement. Cardiac, obstetric, and fetal outcome data were collected. Heart failure was defined according to American College of Cardiology/American Heart Association guidelines[15] as a clinical syndrome characterized by specific symptoms (dyspnea and fatigue) and signs of fluid retention (edema and rales) on physical examination, as judged by the treating provider. An episode of heart failure was only registered when signs or symptoms of heart failure were present that required new treatment, change of treatment, or hospital admission.

A maternal cardiac event was defined as cardiac arrest, cardiac death, new episode of arrhythmia requiring treatment, heart failure, thromboembolic event, endocarditis, hospitalization for other cardiac reasons, or a cardiac intervention. Fetal adverse outcome was defined as fetal death >14 weeks, neonatal death <1 week, low Apgar score, preterm birth, and small for gestational age. Follow-up was available ≤1 week after delivery for all patients. Data on events during 6 months after delivery were collected. However, limited follow-up data at 6 months postpartum were available in some patients (53%) and are therefore reported separately.

Definition of Valve Disease

Mitral valve disease was defined according to the European Association of Echocardiography and American Society of Echocardiography recommendations for echocardiographic assessment of valve stenosis.[16] The severity of mitral valve stenosis (MS) was defined as follows:

- Mild MS = valve area >1.5 cm^2 or if area not available: mean gradient <6 mm Hg
- Moderate MS = valve area 1.0 to 1.5 cm^2 or if area not available: mean gradient 6 to 12 mm Hg
- Severe MS = valve area <1.0 cm^2 or if area not available: mean gradient >12 mm Hg

Mitral valve regurgitation (MR) quantification was based on visual inspection and quantitative measurements and was determined by the treating cardiologist. New York Heart Association (NYHA) classification was used to define whether patients were asymptomatic (NYHA class I) or symptomatic (NYHA class ≥II).

Statistical Analysis

Continuous variables are presented as mean and standard deviation, or median and first and third quartiles (Q1–Q3), and differences among groups were assessed using Student's *t* test or Mann-Whitney test as appropriate. In case of 3 categories (mild, moderate, severe stenosis), 1-way analysis of variance tests were performed or Kruskal-Wallis as appropriate. Categorical variables are presented as frequencies and percentages, and differences were studied using χ^2 or Fisher exact test as appropriate.

We compared pregnancy outcomes of women with isolated mild MR to those with moderate/severe MR. Similarly, we divided women with MS (regardless of whether it was accompanied by MR) into mild, moderate, or severe stenosis and compared the outcomes of these 3 groups. Separate analyses were performed for symptomatic and asymptomatic patients and for patients from countries with emerging or advanced economies. Patients with isolated moderate/severe MS were compared with those with moderate/severe mixed mitral valve disease (MS+MR). Uni- and multivariable logistic regression analyses were performed to search for predictors of maternal cardiac events and adverse fetal outcomes. Possible new predictors were identified by performing univariable logistic regression analyses. All variables with a *P* value <0.10 in univariable analyses were entered into multivariable logistic regression analysis. Generalized linear mixed models were used as a result of the multilevel structure in the data. The ROPAC database consists of 2 levels: patients (level 1) were nested in centers (level 2), and centers were nested in countries (level 3). To account for differences in outcomes among countries and among centers, random effects for country and center were added to the model. Patient and country characteristics were entered as fixed effects. Odds ratios and 95% confidence intervals are provided. Statistical tests were considered significant if a *P* value was <0.05 (2-sided). All analyses, except for multilevel modeling, were performed with SPSS version 21.0 (IBM Corp). Multilevel modeling was performed in R V.3.1, package lme4.

RESULTS

Of the 2966 patients included in the ROPAC registry from January 2008 to April 2014, 390 women had rheumatic mitral valve disease. Mean age was 28.9 years (±6.0), and 103 women (26.4%) were primigravida. The majority lived in countries with an emerging economy (75.4%), and they were known to have mitral valve disease before pregnancy (75.1%). The type of mitral valve disease is presented in Figure 1. MS with or without MR was present in 273 women, whereas 117 had MR only. The grade of MS was mild in 57 (20.9%), moderate in 107 (39.2%), severe in 54 (19.8%), and unknown in 55 (20.1%). The grade of MR in patients with isolated MR (in the absence of stenosis) was mild in 43 (36.8%), moderate in 35 (29.9%), severe in 30 (25.6%), and unknown in 9 (7.7%). Note that for 64 patients of the total cohort, severity of valve disease was unknown, which explains discrepancies in numbers mentioned in the text and tables. Baseline characteristics are presented in Table 1, stratified for severity of disease. Before pregnancy, a percutaneous or surgical valve repair had been performed in 26.9% of all patients but in fewer patients with MR and severe MS. Women with MS had signs of heart failure before pregnancy more often than women with only MR (34.1% versus 10.3%, *P*=0.019), and in particular those with moderate or severe MS. Women with MS also received cardiac medication before pregnancy more often than women with MR (38.6% versus 24.8%, *P*=0.009).

Outcomes of pregnancy are presented in Tables 2 and 3 and will be discussed separately for MS and MR. Caesarean section was performed in the majority of women (52%). In a large proportion of these women, Caesarean section was planned for an obstetric reason. In 20% of women, a Caesarean section was planned in advance for a cardiac reason.

Mitral Valve Stenosis

The outcomes of pregnancy are presented in Tables 2 and 3, stratified for mild, moderate, and severe stenosis. Maternal death during pregnancy occurred in 1 patient with MS (1.9% of severe MS). This patient died at 35 weeks of pregnancy because of acute heart failure. Two other women died during follow-up (between 1 week and 6 months postpartum). One of these 2 women was a patient with severe MS (5.3% of patients with severe MS available for follow-up), who died 2 weeks after spontaneous abortion, complicated by sepsis, atrial fibrillation, and cardiogenic shock. The other patient had moderate MS (1.7% of patients with moderate MS available for follow-up) and developed atrial fibrillation treated with heparin peripartum, which was discontinued because of hemorrhage of the Caesarean section wound. In the second week postpartum, she developed sudden severe abdominal pain and dyspnea, and she died after a cardiac arrest. An aortic embolism or acute mesenteric vascular occlusion was suspected, but autopsy was denied.

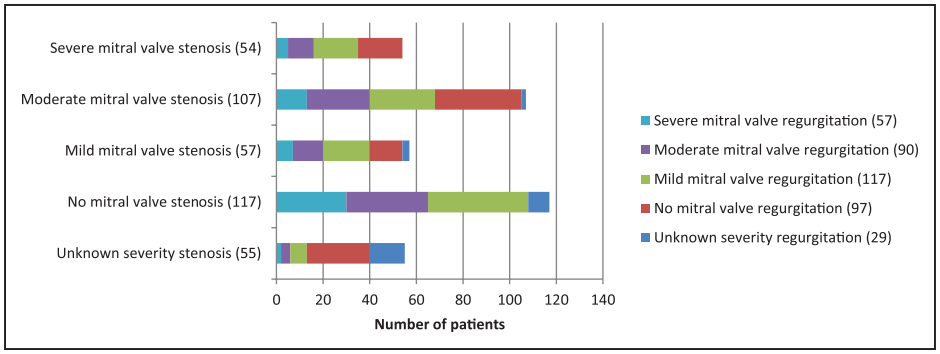

Figure 1. Severity of rheumatic mitral valve disease.

Of all patients with MS, hospital admission for a cardiac reason was required in 23.1% during pregnancy. The main reason was heart failure, in particular in women with severe MS (49.1%). The risk was also significant in moderate MS: 31.8% developed heart failure (22.0% of previously asymptomatic women with moderate MS and 41.1% of previously symptomatic women with moderate MS; *P*=0.036). Timing of heart failure in patients with MS was 71% during pregnancy only, 14% during pregnancy and ≤1 week after delivery, and 15% after delivery only. Episodes of heart failure in the presence of MS were treated mainly with diuretics (59.5%), β-blockers (41.2%), or ACE-inhibitors (4.7%).

A cardiac intervention was performed during pregnancy in 15 patients with MS (5.9%): 14 patients had percutaneous balloon mitral commissurotomy, and 1 patient had a surgical valve replacement. Timing of intervention was during the first trimester in 2 patients, second trimester in 7 patients, and third trimester in 4 patients (and unknown in 2). The course of pregnancy was uneventful after these interventions. Women with MS from countries with an advanced economy had an intervention during pregnancy more often than those from countries with an emerging economy (11.4% versus 3.1%, *P*=0.015), and this difference persisted when assessing women with isolated MS only (19.4% versus 4.9%, *P*=0.036).

Figure I in the online-only Data Supplement depicts outcomes of pregnancy in women with MS who had had valve intervention before pregnancy (n=69) versus those who had not (n=149). There were no major differences, except for women with severe MS: women with an intervention before pregnancy had significant fewer adverse cardiac events than those without prior intervention (14% versus 66%, *P*=0.014).

Table 1. Baseline Characteristics of Patients With Rheumatic Mitral Valve Disease

Baseline Characteristics	Rheumatic Mitral Valve Disease, All (n=390)	Mitral Regurgitation (No Mitral Stenosis)			Mitral Stenosis (With or Without Mitral Regurgitation)			
		Mild (n=43)	Moderate or Severe (n=65)	*P* Value	Mild (n=57)	Moderate (n=107)	Severe (n=54)	*P* Value
Age, y (±SD)	28.9 (±6.0)	29.2 (±6.8)	28.1 (±5.2)	0.32	28.9 (±6.2)	29.8 (±5.8)	27.5 (±6.0)	0.07
Living in an emerging country	294 (75.4)	36 (83.7)	58 (89.2)	0.40	39 (68.4)	77 (72.0)	46 (85.2)	0.096
Primigravida	103 (26.4)	7 (16.3)	13 (20.0)	0.63	19 (33.3)	26 (24.3)	23 (42.6)	0.06
Twin pregnancy	15 (4.1)	0 (0.0)	4 (6.8)	0.14	1 (1.9)	5 (4.9)	2 (4.3)	0.72
Current smoking	7 (1.9)	1 (2.3)	0 (0.0)	0.40	3 (5.6)	1 (1.0)	0 (0.0)	0.13
Prior diabetes mellitus	5 (1.3)	1 (2.3)	0 (0.0)	0.40	1 (1.8)	0 (0.0)	0 (0.0)	0.51
Prior hypertension	14 (3.6)	2 (4.8)	4 (6.3)	1.00	3 (5.3)	4 (3.7)	0 (0.0)	0.32
Prior intervention	105 (26.9)	4 (9.3)	7 (10.8)	1.00	22 (38.6)	40 (37.4)	7 (13.0)	0.003
Signs of heart failure before pregnancy	81 (21.0)	1 (2.3)	13 (20.0)	0.007	7 (12.3)	25 (23.6)	18 (34.0)	0.026
Atrial fibrillation before pregnancy	26 (6.7)	1 (2.3)	2 (3.1)	1.00	2 (3.5)	8 (7.5)	4 (7.7)	0.63
Cardiac medication before pregnancy	134 (34.4)	8 (18.6)	18 (27.7)	0.28	14 (24.6)	48 (44.9)	16 (30.2)	0.022
Right ventricular systolic pressure >30 mm Hg	121 (31.4)	1 (2.3)	21 (32.8)	<0.001	20 (35.7)	43 (41.0)	23 (42.6)	0.73
Any mitral valve regurgitation	292 (75.1)	43 (100)	65 (100)	na	43 (75.4)	70 (65.4)	35 (64.8)	0.36

Values are n (%). na indicates not applicable. Unknown severity of disease: n=64. This value explains the discrepancies between the total group and the subgroups.

Table 2. Maternal Outcomes of Pregnancy

Baseline Characteristics	Rheumatic Mitral Valve Disease, All (n=390)	Mitral Regurgitation (No Mitral Stenosis)			Mitral Stenosis (With or Without Mitral Regurgitation)			
		Mild (n=43)	Moderate or Severe (n=65)	*P* Value	Mild (n=57)	Moderate (n=107)	Severe (n=54)	*P* Value
Maternal mortality ≤ 1 wk postpartum	1 (0.3)	0 (0.0)	0 (0.0)	na	0 (0.0)	0 (0.0)	1 (1.9)	0.25
Hospital admission for a cardiac reason	79 (20.3)	2 (4.7)	13 (20.0)	0.024	9 (15.8)	25 (23.4)	18 (33.3)	0.09
Heart failure	104 (26.7)	3 (7.0)	15 (23.1)	0.029	9 (15.8)	34 (31.8)	26 (48.1)	0.001
Cardiac intervention performed	16 (4.1)	0 (0.0)	0 (0.0)	na	0 (0.0)	4 (3.7)	8 (14.8)	0.002
Supraventricular tachycardia	17 (4.4)	0 (0.0)	1 (1.5)	1.00	1 (1.8)	6 (5.6)	4 (7.4)	0.40
Ventricular tachycardia	1 (0.3)	0 (0.0)	0 (0.0)	na	0 (0.0)	1 (0.9)	0 (0.0)	1.00
Thrombotic complication	1 (0.3)	0 (0.0)	0 (0.0)	na	0 (0.0)	1* (0.9)	0 (0.0)	1.00
Pregnancy-induced hypertension	7 (1.8)	2 (4.7)	2 (3.1)	1.00	1 (1.8)	2 (1.9)	0 (0.0)	1.00
(Pre-) eclampsia or HELLP	6 (1.5)	0 (0.0)	1 (1.5)	1.00	2 (3.5)	0 (0.0)	1 (1.9)	0.13
Postpartum hemorrhage	10 (2.6)	0 (0.0)	1 (1.5)	1.00	3 (5.3)	4 (3.7)	1 (1.9)	0.66
Follow-up after 6 mo	205 (52.6)	18 (41.9)	26 (40.0)	1.00	37 (64.9)	58 (54.2)	19 (35.2)	0.006
Mortality after 1 wk, <6 mo	3 (1.5)	0 (0.0)	1 (3.8)	1.00	0 (0.0)	1 (1.7)	1 (5.3)	0.41

Values are n (%). HELLP indicates hemolysis elevated liver enzymes low platelet count; and na, not applicable. Unknown severity of disease: n=64. No maternal mortality occurred in this group.

*Cerebrovascular accident.

Miscarriage or fetal death was reported in 5.1% of all women with MS versus 3.4% of women with MR (*P*=0.46). Women with MS gave birth to babies small for gestational age more often than women with MR (14.0% versus 3.5%, *P*=0.009). Women with severe MS delivered earlier (*P*=0.041), and their babies had a lower birth weight (*P*=0.007).

The outcomes of women with moderate or severe MS in the presence and absence of significant MR are presented in Table 4. Women with mixed mitral valve disease were more likely to have pulmonary hypertension before pregnancy than women with isolated MS (48.2% versus 23.6%, *P*=0.007). A cardiac intervention was performed only in patients with isolated MS (0% versus 12.5%, *P*=0.013). The outcomes of pregnancy were not different in mixed mitral valve disease compared with isolated MS.

Isolated Mitral Valve Regurgitation

One patient with severe MR died (3.8% of patients available for follow-up) (Table 2). She was asymptomatic before pregnancy and had normal left ventricular function. She developed cardiogenic shock predelivery at 39 weeks, with the subsequent perinatal death of her child. Unfortunately, further details about the course of her pregnancy and specifically the reason for deterioration are not available. Urgent surgical valve repair was planned directly after pregnancy, but she discharged herself against medical advice, and she died weeks later because of cardiogenic shock. Hospital admission for any cardiac reason was required in 13.7% of women with MR mainly because of heart failure, which occurred in 16.2% compared with 31.1% of patients with MS (*P*=0.002). Heart failure in the presence of MR was treated mainly with diuretics (47.4%); some received β-blockers (15.8%) or ACE inhibitors (5.3%). Surgical valve replacement was performed in 1 patient (0.9% of patients with MR) after 10 weeks of gestation. She received a mechanical valve and was treated with vitamin K throughout pregnancy, with a switch to heparin before vaginal delivery, with good fetal outcome. Outcomes of pregnancy are stratified for emerging and advanced economies in Table I in the online-only Data Supplement.

Symptomatic Patients

Before pregnancy, 168 patients (43.1%) were in NYHA class >I as shown in Table 5. In this table, comparison was made for women who were symptomatic before pregnancy versus those who were asymptomatic before pregnancy. Compared with prepregnancy asymptomatic patients (n=217), symptomatic women more frequently had signs of heart failure, had signs of pulmonary hypertension, took cardiac medications, and had severe MS. During pregnancy, hospital admission was required in 33.3% of symptomatic patients, mainly for heart failure, but also for supraventricular arrhythmias. The majority of cardiac interventions were performed in the group that was symptomatic before pregnancy. A higher incidence of babies small for gestational age was found in mater-

Table 3. Obstetric and Fetal Outcomes of Pregnancy

Obstetric and Fetal Outcome	Rheumatic Mitral Valve Disease, All (n=390)	Mitral Regurgitation (No Mitral Stenosis)			Mitral Stenosis (With or Without Mitral Regurgitation)			
		Mild (n=43)	Moderate or Severe (n=65)	*P* Value	Mild (n=57)	Moderate (n=107)	Severe (n=54)	*P* Value
Caesarean section	199 (52.4)	15 (36.6)	28 (45.2)	0.39	28 (50.0)	67 (63.2)	31 (60.8)	0.26
Emergency caesarean section for cardiac reason	12 (3.1)	1 (2.3)	2 (3.1)	1.00	0 (0.0)	3 (2.8)	5 (9.4)	0.024
Abortus provocatus								
Maternal reason	2 (0.5)	0 (0.0)	1 (1.5)	1.00	0 (0.0)	0 (0.0)	0 (0.0)	na
Fetal reason	1 (0.3)	0 (0.0)	0 (0.0)	na	0 (0.0)	0 (0.0)	0 (0.0)	na
Miscarriage <24 wk	14 (3.6)	0 (0.0)	3 (4.6)	0.27	2 (3.5)	4 (3.7)	3 (5.6)	0.82
Fetal death ≥24 wk	4 (1.0)	0 (0.0)	1 (1.5)	1.00	0 (0.0)	1 (0.9)	1 (1.9)	0.74
Low Apgar (<7)	25 (8.1)	4 (12.1)	1 (2.5)	0.17	3 (6.5)	5 (5.6)	5 (11.9)	0.45
Preterm birth	33 (9.5)	0 (0.0)	2 (3.6)	0.51	2 (3.8)	9 (9.3)	10 (21.3)	0.015
Birthweight <2500 g	64 (16.4)	5 (11.6)	4 (6.2)	0.48	4 (7.0)	18 (16.8)	17 (31.5)	0.003
Small for gestational age	36 (11.3)	0 (0.0)	3 (6.8)	0.26	2 (4.3)	10 (10.8)	9 (19.6)	0.06
Median pregnancy duration, weeks (Q1–Q3)	39.0 (38.0–39.6)	39.0 (38.3–39.9)	39.0 (38.3–39.4)	0.29	39.0 (38.3–39.9)	39.0 (38.0–39.4)	38.7 (37.0–39.3)	0.041
Median birthweight, g (Q1–Q3)	2900 (2610–3100)	3050 (2750–3300)	2925 (2750–3110)	0.09	2925 (2690–3200)	2900 (2640–3100)	2700 (2400–3000)	0.007

Values are n (%). na indicates not applicable; and Q1–Q3, first through third quartiles. Unknown severity of disease: n=64. No maternal mortality occurred in this group.

nal patients who were symptomatic versus asymptomatic before pregnancy (15.1% versus 7.7%, *P*=0.038).

Predictors of Adverse Outcomes

Results of uni- and multivariable logistic regression analyses are presented in Figure 2. Prepregnancy NYHA class >I was an independent predictor of maternal cardiac events in women with MS. Severe MS was independently associated with adverse fetal outcomes. Further details are presented in Tables II and III in the online-only Data Supplement.

A list of countries that included women with rheumatic mitral valve disease can be found in Table IV in the online-only Data Supplement.

DISCUSSION

This international prospective registry studies the outcomes of pregnancy in women with rheumatic mitral valve disease. It provides contemporaneous data showing that women with mild and asymptomatic rheumatic mitral valve disease tolerate pregnancy well, but that morbidity is high especially in women with severe mitral valve stenosis. Heart failure occurred in ≤48% of women with severe MS, and patients with prepregnancy NYHA class >I were at particularly high risk of maternal cardiac events. This finding is not surprising because pregnancy induces an expansion of the plasma volume, which is poorly tolerated in the presence of severe left-sided stenosis. The stenotic mitral valve compromises the ability of the heart to increase cardiac output, increasing left atrial and pulmonary pressures and resulting in cardiac failure. In addition, an increase in cardiac output is required to provide sufficient uteroplacental blood flow; when this flow is compromised, fetal growth may be reduced.[17]

Mitral Valve Stenosis

Although mild MS is usually well tolerated with pregnancy, this study revealed that women with mild disease had a significant risk of heart failure of 15.8%, whereas those with moderate and severe disease had risks of 31.8% and 48.1%, respectively. These data are consistent with an earlier smaller study (80 women with rheumatic valve stenosis), which reported pulmonary edema in mild (24%), moderate (34%), and severe (56%) MS during pregnancy,[18] although the event rates in the current study were lower than in another study of 46 women with mixed mitral valve disease.[19] The degree of stenosis, together with NYHA class and possibly right ventricular systolic pressure in those with mild or moderate MS, may help to distinguish between women who are likely to tol-

Table 4. Isolated Mitral Valve Stenosis Versus Mixed Mitral Valve Disease

	Isolated Moderate or Severe Mitral Stenosis (n=56)	Moderate or Severe Mitral Stenosis Combined With Moderate or Severe Mitral Regurgitation (n=56)	*P* Value
Baseline Characteristics			
Age, y (SD)	30.0 (±5.8)	28.5 (±6.2)	0.18
Living in an emerging country	39 (69.6)	46 (82.1)	0.12
Primigravida	17 (30.4)	15 (26.8)	0.68
Prior intervention	18 (32.1)	16 (28.6)	0.68
Signs of heart failure before pregnancy	15 (26.8)	15 (27.8)	0.91
Atrial fibrillation before pregnancy	6 (10.7)	5 (9.1)	0.78
Cardiac medication before pregnancy	25 (44.6)	21 (38.2)	0.49
Right ventricular systolic pressure >30 mm Hg	13 (23.6)	27 (48.2)	0.007
Severe mitral valve stenosis	19 (33.9)	16 (28.6)	0.54
Pregnancy outcome			
Maternal mortality, 1 wk postpartum	0 (0.0)	0 (0.0)	na
Hospital admission for a cardiac reason	16 (28.3)	13 (23.2)	0.52
Heart failure	24 (42.9)	19 (33.9)	0.33
Supraventricular tachycardia	6 (10.7)	3 (5.4)	0.49
Cardiac intervention performed	7 (12.5)	0 (0.0)	0.013
Caesarean section	30 (55.6)	36 (65.5)	0.29
Emergency caesarean section for a cardiac reason	3 (5.4)	5 (8.9)	0.72
Miscarriage <24 wk	1 (1.4)	5 (8.9)	0.21
Fetal death ≥24 wk	1 (1.8)	0 (0.0)	1.00
Low Apgar (<7)	2 (4.1)	5 (12.5)	0.24
Preterm birth	10 (19.2)	5 (10.2)	0.20
Birthweight <2500 g	11 (19.6)	14 (25.0)	0.50
Small for gestational age	6 (11.8)	5 (11.1)	0.92
Median pregnancy duration, wk (Q1–Q3)	38.4 (37.0–39.4)	38.9 (38.0–39.3)	0.43
Median birthweight, g (Q1–Q3)	2800 (2600–3100)	2775 (2500–3000)	0.44
Follow-up after 6 mo	24 (42.9)	24 (42.9)	1.00
Mortality after 1 wk, <6 mo	0 (0.0)	2 (8.3)	0.49

Values are n (%). na indicates not applicable; and Q1–Q3, first through third quartiles. Note that for 49 patients, the severity of concomitant mitral regurgitation was unknown; therefore, these women were not included in this table. This explains the discrepancies between numbers in Tables 3 and 4.

erate pregnancy well and those who have an unacceptably high risk of pregnancy complications. We found that NYHA class ≥II was an independent predictor of maternal cardiac events during pregnancy. A previous prospective study reporting on pregnancy outcome in 192 patients with rheumatic heart disease, including 61% with a mitral valve lesion, also found that heart failure (7% versus 49%) and arrhythmic (2% versus 21%) events occurred more often in women with NYHA class III or IV than in women with NYHA class I or II.[20] Echocardiographic follow-up during pregnancy is important to detect early hemodynamic changes that may precede and possibly predict clinical deterioration. In women with severe mitral valve stenosis and NYHA class III or IV, an increase of pulmonary capillary wedge pressure immediately postpartum has been described.[21] In our study, 30% of the cases developing heart failure in the presence of MS occurred in the first week after delivery, regardless of whether it was preceded by an episode during pregnancy. Thus, close monitoring of the hemodynamic situation intrapartum and in the first days after delivery is essential, and efforts should be made to limit large fluctuations in pre- and afterload. Heart failure should be treated just as in nonpregnant patients with mitral valve disease. Only 40% of women with MS and heart failure were treated with β-blockers, despite the fact that β-blockers are well recognized to be an important component of the management of heart failure in the presence of MS. This finding emphasizes the gap between guideline recommendations and clinical implementation as well as the need for wider education.

It is noteworthy that 75% of women were known to have mitral valve disease before pregnancy. A third

Table 5. Baseline and Pregnancy Outcomes in Asymptomatic and Symptomatic Patients

	Asymptomatic (n=217)	Symptomatic (n=168)	*P* Value
Baseline Characteristics			
Age, y (SD)	29.2 (±6.2)	28.4 (±5.7)	0.17
Living in an emerging country	162 (74.7)	130 (77.4)	0.54
Primigravida	46 (21.2)	55 (32.7)	0.011
Prior intervention	61 (28.1)	43 (25.6)	0.58
Signs of heart failure before pregnancy	3 (1.4)	77 (46.4)	<0.001
Atrial fibrillation before pregnancy	12 (5.6)	13 (7.8)	0.37
Cardiac medication before pregnancy	60 (27.8)	72 (42.9)	0.002
Right ventricular systolic pressure >30 mm Hg	48 (22.3)	72 (43.6)	<0.001
Severe mitral valve regurgitation*	27 (17.2)	28 (18.4)	0.18
Severe mitral valve stenosis*	21 (11.1)	31 (22.0)	0.007
Pregnancy outcome			
Maternal mortality, ≤1 wk postpartum	0 (0.0)	1 (0.6)	0.44
Hospital admission for a cardiac reason	21 (9.7)	56 (33.3)	<0.001
Heart failure	42 (19.4)	60 (35.7)	<0.001
Supraventricular tachycardia	4 (1.8)	12 (7.1)	0.010
Cardiac intervention performed	3 (1.4)	13 (7.7)	0.002
Caesarean section	102 (47.9)	93 (57.4)	0.07
Emergency caesarean section for a cardiac reason	3 (1.4)	7 (4.2)	0.11
Miscarriage <24 wk	8 (3.7)	6 (3.6)	0.95
Fetal death ≥24 wk	2 (0.9)	2 (1.2)	1.00
Low Apgar (<7)	12 (7.5)	11 (7.8)	0.91
Preterm birth	19 (9.7)	12 (8.1)	0.59
Birthweight <2500 g	31 (14.3)	31 (18.5)	0.27
Small for gestational age	13 (7.7)	22 (15.1)	0.038
Median pregnancy duration, wk (Q1–Q3)	39.0 (38.0–39.6)	39.0 (38.0–39.6)	0.21
Median birthweight, g (Q1–Q3)	2900 (2658–3188)	2900 (2600–3000)	0.10
Follow-up after 6 mo	104 (47.9)	100 (59.5)	0.024
Mortality after 1 wk, <6 mo	1 (1.0)	2 (2.0)	0.62

Values are n (%). Q1–Q3 indicates first and third quartiles.
*Percentage of patients with known severity of disease.

of all women with MS were symptomatic before pregnancy, and half of the women with severe MS went on to need hospital admission for heart failure during their pregnancy, representing significant morbidity and cost. One could speculate that if those patients with isolated severe mitral stenosis had undergone percutaneous balloon mitral commissurotomy preconception, they would have had a lower risk pregnancy with less chance of morbidity and hospital admission.

We have shown a remarkable difference in birth weight and pregnancy duration between emerging and advanced economies. Our data are a reflection of the practitioner's influence on pregnancy outcomes: physicians from advanced economies are eager to induce labor for the benefit of the mother. However, this approach did not result in a significant difference in maternal outcomes, although this conclusion is partly restricted by low numbers. A high number of planned Caesarean sections occurred, which is alarming because the current literature[22] shows no evidence of a clear benefit of Caesarean section over a vaginal delivery in women with heart disease.

Valve Intervention During Pregnancy

Sixteen women, almost all of them with MS, had an intervention during pregnancy, most commonly (14 of 16 cases) with a percutaneous balloon mitral commissurotomy. This treatment option is effective for selected patients with isolated mitral valve stenosis, with a rapid decrease of left atrial pressure and pulmonary artery pressure.[2] Percutaneous balloon mitral commissurotomy is effective and safe during pregnancy[23] and is preferred to a surgical procedure because the latter still carries a risk of fetal

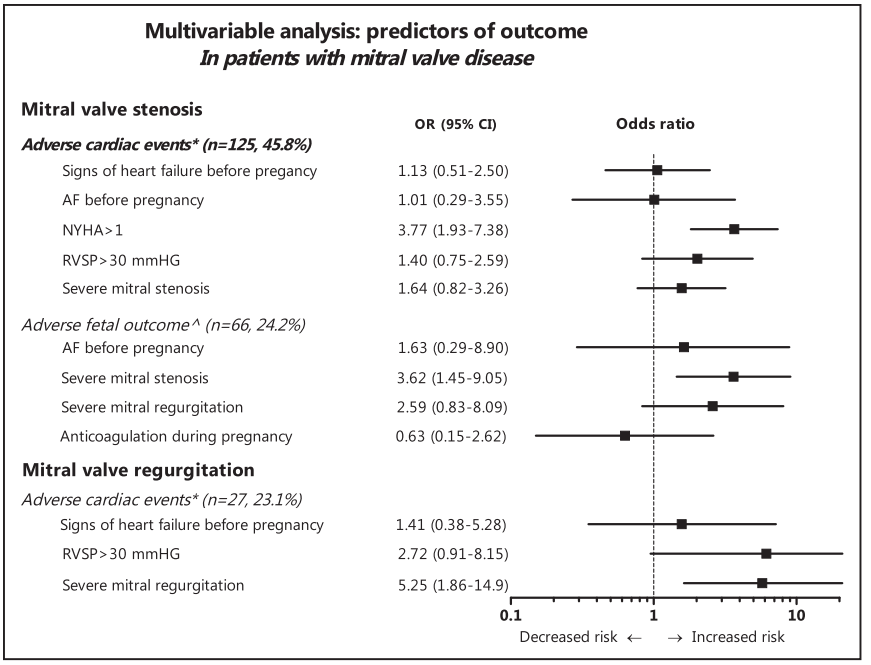

Figure 2. Predictors of outcome. AF indicates atrial fibrillation; CI, confidence interval; OR, odds ratio; NYHA, New York Heart Association; and RVSP, right ventricular systolic pressure. *Defined as cardiac arrest, cardiac death, new episode of arrhythmia requiring treatment, heart failure, thromboembolic event, endocarditis, hospitalization for cardiac reason, or cardiac intervention. ^Defined as fetal death after 14 weeks, neonatal death <1 week, low Apgar score, preterm birth, and small for gestational age

demise of ≈20%.[24] However, patients with severe MS in the presence of significant MR are less suitable for a percutaneous intervention.[25] Treating patients with severe symptomatic mixed disease during pregnancy is complex, and evidence-based recommendations on the approach are lacking. Indeed, in our study, 2 women with mixed disease died in the second week after pregnancy.

Despite that more women from emerging countries had severe MS, the number of valvular interventions was greater in countries with an advanced economy probably because of the greater access in these countries.[3] Enhanced flowcharts for the choice of intervention in women with valve disease in different settings have been proposed.[26] Although, ideally, any percutaneous or surgical intervention should be undertaken before conception, the threshold for intervention during pregnancy, particularly for percutaneous balloon mitral commissurotomy in isolated severe mitral stenosis, should be low. The best timing for intervention has been suggested to be after the fourth month.[11]

Isolated Mitral Valve Regurgitation

Mild MR is generally classified as a modified World Health Organization pregnancy risk class I (no detectable increased risk of maternal mortality and no or mild increased risk of morbidity).[11] The results of this study support this classification, with low maternal and fetal morbidity. Also, moderate to severe MR is often seen as benign. However, in our study, it was associated with a surprisingly high rate of heart failure (23%) and should therefore not be underestimated. As commented on earlier, there are marked changes in hemodynamic function during pregnancy,[27,28] which may be poorly tolerated in the context of substantial MR. There is little evidence regarding the outcomes of pregnancy in this group of women. In congenital heart disease, the presence of severe atrioventricular valve disease is a predictor of adverse outcomes.[29] In previous studies concerning rheumatic valve disease in general, mainly women with symptomatic regurgitation were at risk,[20] which is confirmed by our results.

Clinical Implications

Mortality and cardiac deterioration in this cohort could have been reduced by appropriate prepregnancy assessment and intervention as suggested by the guidelines.[25] A delay in patients seeking help is often the main contributing factor to maternal cardiovascular death in emerging countries,[6] which may contribute to the previously described high maternal and fetal mortality in sub-Saharan countries.[30] Hence, adequate counseling of adolescents and young women with rheumatic heart disease about the risks of pregnancy is of utmost importance to convince them to see a cardiologist before getting pregnant. There seems to be a real task here, and this societal issue might need political support.

Also, the question remains how to deal with women with asymptomatic moderate MS, who are not yet candidates for valve intervention but are contemplating pregnancy. Pregnancy in these women is associated with a significant risk of heart failure. Most of these women seem to have favorable clinical and probably also anatomic conditions for percutaneous balloon mitral commissurotomy. Therefore, the availability of a low-risk intervention is an incentive to consider wide indications of percutaneous balloon mitral commissurotomy in young women with moderate or severe MS who have a desire for pregnancy, even if they are asymptomatic.

Limitations

Definition of valve disease varies between the different guidelines and is subject to updating in newer versions of the guidelines. We were restricted to the guidelines used when the majority of the patients were included.[16,25] However, having symptoms of valve disease has direct consequences with regard to intervention in current guidelines,[31] which is why we decided to perform a subanalysis in patients with and without symptoms. Physiological symptoms of pregnancy may be difficult to distinguish from significant heart failure symptoms, which should be taken into account when interpreting our results. This study was conducted from a voluntary registry, and therefore potential reporting bias should be taken into account when interpreting the results. Furthermore, although follow-up ≤1 week postpartum was complete in all patients, follow-up until 6 months postpartum was available in only 53% of the patients, and therefore postpartum adverse events may be underestimated.

One of the major challenges in large registries is incomplete data: in this cohort, the severity of disease was unknown for 64 patients. In our cohort, mitral valve area, mean gradient, and pressure half time were available in some patients and at different time points, which hampered statistical analysis to study their potential value as predictors of adverse outcomes. Finally, of the 75% of women from emerging countries, the majority came from Egypt. Therefore, the results likely do not reflect the outcomes for women living in even more disadvantaged parts of the world, such as sub-Saharan Africa. In this study, most patients (75%) were diagnosed to have rheumatic heart disease before pregnancy and had access to cardiac care. Patients in very low-income areas presenting late in pregnancy with severe disease probably have an even worse outcome, and more work is clearly needed to understand the impact of rheumatic heart disease in pregnancy in these areas.

CONCLUSION

Women with moderate or severe rheumatic MS who were symptomatic before pregnancy are at significant risk of complications during pregnancy. In particular, women with symptomatic or severe MS should be advised against pregnancy until valve intervention has taken place. Women with mild stenosis and those with more than mild MR should be adequately counseled about the risk of complications, although a large part of this group will be brought safely to term and deliver a healthy baby. Close follow-up during pregnancy will allow early recognition of symptoms and timely intervention to avoid an unfavorable maternal or fetal outcome.

ARTICLE INFORMATION

Received November 6, 2017; accepted January 9, 2018.

The online-only Data Supplement is available with this article at http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIRCULATIONAHA.117.032561/-/DC1.

Correspondence

Jolien W. Roos-Hesselink, MD, PhD, Erasmus MC, Thoraxcenter, Department of Cardiology, PO Box 2040, 3000 CA Rotterdam, the Netherlands. E-mail j.roos@erasmusmc.nl

Affiliations

Department of Cardiology, Erasmus MC, Rotterdam, the Netherlands (I.M.v.H., J.W.R.-H.). Department of Cardiology, Adult Congenital Heart Disease Unit, Queen Elizabeth Hospital, Birmingham, United Kingdom (S.A.T.). Department of Cardiology, Faculty of Medicine, El Minya University Hospital, Minya, Egypt (N.T.). Department of Cardiology, Kasr Al Ainy Hospital, Cairo University, Egypt (G.Y.). Department of Cardiology, Banha University Hospital, Egypt (A.E.). Department of Cardiology, Medical University of Vienna, Austria (H.G.). Department of Cardiology, Alexandria University Students Hospital, Alexandria, Egypt (Y.E.R.). Department of Cardiology, Bichat Hospital, AP-HP, DHU Fire and Paris Diderot University, France (B.I.). Department of Obstetrics, Imperial College School of Medicine, Chelsea and Westminster Hospital, London, United Kingdom (M.R.J.). Department of Cardiology, Norwich Medical School, University of East Anglia, Norwich, United Kingdom (R.H.). Fellow of the ESC, Sophia Antipolis Cedex, Biot, France (J.W.R.-H.).

Acknowledgments

The authors thank Sara Baart from the Department of Cardiology, Erasmus MC, Rotterdam, the Netherlands, for her support in the statistical analysis; all ROPAC investigators listed in the online-only Data Supplement; and the EORP team for their contribution, in particular Elin Folkesson Lefrancq (project officer) and Viviane Missiamenou (data manager). To join the registry, visit http://www.escardio.org/guidelines-surveys/eorp/surveys/pregnancy/Pages/welcome.aspx.

Sources of Funding

Since the start of EORP, the following companies have supported the program: Abbott Vascular International (2011–2014), Amgen Cardiovascular (2009–2018), AstraZeneca (2014–2017), Bayer (2009–2018), Boehringer Ingelheim (2009–2016), Boston Scientific (2009–2012), The Bristol Myers Squibb and Pfizer Alliance (2011–2016), The Alliance Daiichi Sankyo Europe GmbH and Eli Lilly and Company (2011–2017), Edwards (2016–2019), Gedeon Richter Plc. (2014–2017), Menarini International (2009–2012), Merck Sharp & Dohme–Merck & Co. (2011–2014), Novartis Pharma AG (2014–2017), ResMed (2014–2016), Sanofi (2009–2011), and SERVIER (2010–2018). The companies that support EORP were not involved in any part of the study or this article.

Disclosures

Dr Iung reports personal fees from Boehringer Ingelheim and Edwards Lifesciences outside the submitted work.

REFERENCES

1. Carapetis JR, Beaton A, Cunningham MW, Guilherme L, Karthikeyan G, Mayosi BM, Sable C, Steer A, Wilson N, Wyber R, Zühlke L. Acute rheumatic fever and rheumatic heart disease. *Nat Rev Dis Primers*. 2016;2:15084. doi: 10.1038/nrdp.2015.84.
2. Remenyi B, ElGuindy A, Smith SC Jr, Yacoub M, Holmes DR Jr. Valvular aspects of rheumatic heart disease. *Lancet*. 2016;387:1335–1346. doi: 10.1016/S0140-6736(16)00547-X.
3. Zühlke L, Engel ME, Karthikeyan G, Rangarajan S, Mackie P, Cupido B, Mauff K, Islam S, Joachim A, Daniels R, Francis V, Ogendo S, Gitura B, Mondo C, Okello E, Lwabi P, Al-Kebsi MM, Hugo-Hamman C, Sheta SS, Haileamlak A, Daniel W, Goshu DY, Abdissa SG, Desta AG, Shasho BA, Begna DM, ElSayed A, Ibrahim AS, Musuku J, Bode-Thomas F, Okeahialam

BN, Ige O, Sutton C, Misra R, Abul Fadl A, Kennedy N, Damasceno A, Sani M, Ogah OS, Olunuga T, Elhassan HH, Mocumbi AO, Adeoye AM, Mntla P, Ojji D, Mucumbitsi J, Teo K, Yusuf S, Mayosi BM. Characteristics, complications, and gaps in evidence-based interventions in rheumatic heart disease: the Global Rheumatic Heart Disease Registry (the REMEDY study). *Eur Heart J*. 2015;36:1115–1122a. doi: 10.1093/eurheartj/ehu449.

4. Roos-Hesselink JW, Ruys TP, Stein JI, Thilén U, Webb GD, Niwa K, Kaemmerer H, Baumgartner H, Budts W, Maggioni AP, Tavazzi L, Taha N, Johnson MR, Hall R; ROPAC Investigators. Outcome of pregnancy in patients with structural or ischaemic heart disease: results of a registry of the European Society of Cardiology. *Eur Heart J*. 2013;34:657–665. doi: 10.1093/eurheartj/ehs270.
5. Watkins DA, Sebitloane M, Engel ME, Mayosi BM. The burden of antenatal heart disease in South Africa: a systematic review. *BMC Cardiovasc Disord*. 2012;12:23. doi: 10.1186/1471-2261-12-23.
6. Soma-Pillay P, Seabe J, Sliwa K. The importance of cardiovascular pathology contributing to maternal death: confidential enquiry into maternal deaths in South Africa, 2011-2013. *Cardiovasc J Afr*. 2016;27:60–65. doi: 10.5830/CVJA-2016-008.
7. Haththotuwa HR, Attygalle D, Jayatilleka AC, Karunaratna V, Thorne SA. Maternal mortality due to cardiac disease in Sri Lanka. *Int J Gynaecol Obstet*. 2009;104:194–198. doi: 10.1016/j.ijgo.2008.10.031.
8. Stout KK, Otto CM. Pregnancy in women with valvular heart disease. *Heart*. 2007;93:552–558. doi: 10.1136/hrt.2005.067975.
9. UN.org. United Nations Millennium Development Goals. http://www.un.org/millenniumgoals.
10. Cantwell R, Clutton-Brock T, Cooper G, Dawson A, Drife J, Garrod D, Harper A, Hulbert D, Lucas S, McClure J, Millward-Sadler H, Neilson J, Nelson-Piercy C, Norman J, O'Herlihy C, Oates M, Shakespeare J, de Swiet M, Williamson C, Beale V, Knight M, Lennox C, Miller A, Parmar D, Rogers J, Springett A. Saving mothers' lives: reviewing maternal deaths to make motherhood safer: 2006–2008. The 8th report of the confidential enquiries into maternal deaths in the United Kingdom. *BJOG*. 2011;118(suppl 1):1–203.
11. Regitz-Zagrosek V, Lundqvist CB, Borghi C, Cifkova R, Ferreira R, Foidart JM, Gibbs JSR, Gohlke-Baerwolf C, Gorenek B, Iung B, Kirby M, Maas AHEM, Morais J, Nihoyannopoulos P, Pieper PG, Presbitero P, Roos-Hesselink JW, Schaufelberger M, Seeland U, Torracca L, Bax J, Auricchio A, Baumgartner H, Ceconi C, Dean V, Deaton C, Fagard R, Funck-Brentano C, Hasdai D, Hoes A, Knuuti J, Kolh P, McDonagh T, Moulin C, Poldermans D, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Torbicki A, Vahanian A, Windecker S, Baumgartner H, Deaton C, Aguiar C, Al-Attar N, Garcia AA, Antoniou A, Coman I, Elkayam U, Gomez-Sanchez MA, Gotcheva N, Hilfiker-Kleiner D, Kiss RG, Kitsiou A, Konings KTS, Lip GYH, Manolis A, Mebaaza A, Mintale I, Morice MC, Mulder BJ, Pasquet A, Price S, Priori SG, Salvador MJ, Shotan A, Silversides CK, Skouby SO, Stein JI, Tornos P, Vejlstrup N, Walker F, Warnes C; Force T and CPG ECPG. ESC guidelines on the management of cardiovascular diseases during pregnancy: The Task Force on the Management of Cardiovascular Diseases during Pregnancy of the European Society of Cardiology (ESC). *Eur Heart J*.. 2011;32:3147–3197.
12. Baumgartner H, Bonhoeffer P, De Groot NM, de Haan F, Deanfield JE, Galie N, Gatzoulis MA, Gohlke-Baerwolf C, Kaemmerer H, Kilner P, Meijboom F, Mulder BJ, Oechslin E, Oliver JM, Serraf A, Szatmari A, Thaulow E, Vouhe PR, Walma E; Task Force on the Management of Grown-Up Congenital Heart Disease of the European Society of Cardiology (ESC); Association for European Paediatric Cardiology (AEPC); ESC Committee for Practice Guidelines (CPG). ESC guidelines for the management of grown-up congenital heart disease (new version 2010). *Eur Heart J*. 2010;31:2915–2957. doi: 10.1093/eurheartj/ehq249.
13. van Hagen IM, Roos-Hesselink JW, Ruys TP, Merz WM, Goland S, Gabriel H, Lelonek M, Trojnarska O, Al Mahmeed WA, Balint HO, Ashour Z, Baumgartner H, Boersma E, Johnson MR, Hall R; ROPAC Investigators and the EURObservational Research Programme (EORP) Team. Pregnancy in women with a mechanical heart valve: data of the European Society of Cardiology Registry of Pregnancy and Cardiac Disease (ROPAC). *Circulation*. 2015;132:132–142. doi: 10.1161/CIRCULATIONAHA.115.015242.
14. International Monetary Fund. *World Economic Outlook - Recovery Strengthens, Remains Uneven*. Washington, DC, April 2014. http://www.imf.org/external/Pubs/ft/weo/2014/01/pdf/text.pdf. Accessed January 26, 2018.
15. Jessup M, Abraham WT, Casey DE, Feldman AM, Francis GS, Ganiats TG, Konstam MA, Mancini DM, Rahko PS, Silver MA, Stevenson LW, Yancy CW. 2009 focused update: ACCF/AHA guidelines for the fiagnosis and management of heart failure in adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. *Circulation*. 2009;119:1977–2016. doi: 10.1161/CIRCULATIONAHA.109.192064.
16. Baumgartner H, Hung J, Bermejo J, Chambers JB, Evangelista A, Griffin BP, Iung B, Otto CM, Pellikka PA, Quiñones M; EAE/ASE. Echocardiographic assessment of valve stenosis: EAE/ASE recommendations for clinical practice. *Eur J Echocardiogr*. 2009;10:1–25. doi: 10.1093/ejechocard/jen303.
17. Kampman MA, Bilardo CM, Mulder BJ, Aarnoudse JG, Ris-Stalpers C, van Veldhuisen DJ, Pieper PG. Maternal cardiac function, uteroplacental Doppler flow parameters and pregnancy outcome: a systematic review. *Ultrasound Obstet Gynecol*. 2015;46:21–28. doi: 10.1002/uog.14697.
18. Silversides CK, Colman JM, Sermer M, Siu SC. Cardiac risk in pregnant women with rheumatic mitral stenosis. *Am J Cardiol*. 2003;91:1382–1385.
19. Hameed A, Karaalp IS, Tummala PP, Wani OR, Canetti M, Akhter MW, Goodwin I, Zapadinsky N, Elkayam U. The effect of valvular heart disease on maternal and fetal outcome of pregnancy. *J Am Coll Cardiol*. 2001;37:893–899.
20. Rezk M, Gamal A. Maternal and fetal outcome in women with rheumatic heart disease: a 3-year observational study. *Arch Gynecol Obstet*. 2016;294:273–278. doi: 10.1007/s00404-015-3990-9.
21. Clark SL, Phelan JP, Greenspoon J, Aldahl D, Horenstein J. Labor and delivery in the presence of mitral stenosis: central hemodynamic observations. *Am J Obstet Gynecol*. 1985;152:984–988.
22. Ruys TP, Roos-Hesselink JW, Pijuan-Domènech A, Vasario E, Gaisin IR, Iung B, Freeman LJ, Gordon EP, Pieper PG, Hall R, Boersma E, Johnson MR; ROPAC Investigators. Is a planned caesarean section in women with cardiac disease beneficial? *Heart*. 2015;101:530–536. doi: 10.1136/heartjnl-2014-306497.
23. Joshi HS, Deshmukh JK, Prajapati JS, Sahoo SS, Vyas PM, Patel IV. Study of effectiveness and safety of percutaneous balloon mitral valvulotomy for treatment of pregnant patients with severe mitral stenosis. *J Clin Diagn Res*. 2015;9:OC14–OC17. doi: 10.7860/JCDR/2015/14765.6923.
24. Pomini F, Mercogliano D, Cavalletti C, Caruso A, Pomini P. Cardiopulmonary bypass in pregnancy. *Ann Thorac Surg*. 1996;61:259–268. doi: 10.1016/0003-4975(95)00818-7.
25. Vahanian A, Alfieri O, Andreotti F, Antunes MJ, Baron-Esquivias G, Baumgartner H, Borger MA, Carrel TP, De Bonis M, Evangelista A, Falk V, Iung B, Lancellotti P, Pierard L, Price S, Schafers HJ, Schuler G, Stepinska J, Swedberg K, Takkenberg J, Von Oppell UO, Windecker S, Zamorano JL, Zembala M; Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology, European Association for Cardio-Thoracic Surgery. Guidelines on the management of valvular heart disease (version 2012). *Eur Heart J*. 2012;33:2451–2496.
26. Sliwa K, Johnson MR, Zilla P, Roos-Hesselink JW. Management of valvular disease in pregnancy: a global perspective. *Eur Heart J*. 2015;36:1078–1089. doi: 10.1093/eurheartj/ehv050.
27. Robson SC, Hunter S, Boys RJ, Dunlop W. Serial study of factors influencing changes in cardiac output during human pregnancy. *Am J Physiol*. 1989;256(4 Pt 2):H1060–H1065. doi: 10.1152/ajpheart.1989.256.4.H1060.
28. Mabie WC, DiSessa TG, Crocker LG, Sibai BM, Arheart KL. A longitudinal study of cardiac output in normal human pregnancy. *Am J Obstet Gynecol*. 1994;170:849–856.
29. Siu SC, Sermer M, Colman JM, Alvarez AN, Mercier LA, Morton BC, Kells CM, Bergin ML, Kiess MC, Marcotte F, Taylor DA, Gordon EP, Spears JC, Tam JW, Amankwah KS, Smallhorn JF, Farine D, Sorensen S; Cardiac Disease in Pregnancy (CARPREG) Investigators. Prospective multicenter study of pregnancy outcomes in women with heart disease. *Circulation*. 2001;104:515–521.
30. Diao M, Kane A, Ndiaye MB, Mbaye A, Bodian M, Dia MM, Sarr M, Kane A, Monsuez JJ, Ba SA. Pregnancy in women with heart disease in sub-Saharan Africa. *Arch Cardiovasc Dis*. 2011;104:370–374. doi: 10.1016/j.acvd.2011.04.001.
31. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP III, Guyton RA, O'Gara PT, Ruiz CE, Skubas NJ, Sorajja P, Sundt TM III, Thomas JD; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014;63:2438–2488. doi: 10.1016/j.jacc.2014.02.537.

Pregnancy Outcomes in Women With Rheumatic Mitral Valve Disease: Results From the Registry of Pregnancy and Cardiac Disease

Iris M. van Hagen, Sara A. Thorne, Nasser Taha, Ghada Youssef, Amro Elnagar, Harald Gabriel, Yahia ElRakshy, Bernard Iung, Mark R. Johnson, Roger Hall and Jolien W. Roos-Hesselink

On behalf of the ROPAC Investigators and EORP Team

Circulation. 2018;137:806-816
doi: 10.1161/CIRCULATIONAHA.117.032561
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7322. Online ISSN: 1524-4539