European Heart Journal (2010) **31**, 2124–2132
doi:10.1093/eurheartj/ehq200



# Predictors of pregnancy complications in women with congenital heart disease

**Willem Drenthen[1]*, Eric Boersma[2], Ali Balci[1], Philip Moons[3], Jolien W. Roos-Hesselink[4], Barbara J.M. Mulder[5,6], Hubert W. Vliegen[7], Arie P.J. van Dijk[8], Adriaan A. Voors[1], Sing C. Yap[4], Dirk J. van Veldhuisen[1], and Petronella G. Pieper[1] On behalf of the ZAHARA Investigators**

[1]Department of Cardiology, University Medical Centre Groningen, University of Groningen, PO Box 30.001, 9700 RB Groningen, The Netherlands; [2]Department of Epidemiology, Erasmus Medical Centre, Rotterdam, The Netherlands; [3]Department of Cardiology, University Hospitals Leuven, Leuven, Belgium; [4]Department of Cardiology, Erasmus Medical Centre, Rotterdam, The Netherlands; [5]Department of Cardiology, Academic Medical Centre, Amsterdam, The Netherlands; [6]Department of Cardiology, University Hospital Utrecht, Utrecht, The Netherlands; [7]Department of Cardiology, Leiden University Medical Centre, Leiden, The Netherlands; and [8]Department of Cardiology, Radboud University Medical Centre Nijmegen, Nijmegen, The Netherlands

*Received 30 November 2009; revised 26 April 2010; accepted 10 May 2010; online publish-ahead-of-print 28 June 2010*

**Aims** Data regarding pregnancy outcome in women with congenital heart disease (CHD) are limited.

**Methods and results** In 1802 women with CHD, 1302 completed pregnancies were observed. Independent predictors of cardiac, obstetric, and neonatal complications were calculated using logistic regression. The most prevalent cardiac complications during pregnancy were arrhythmias (4.7%) and heart failure (1.6%). Factors independently associated with maternal cardiac complications were the presence of cyanotic heart disease (corrected/uncorrected) ($P < 0.0001$), the use of cardiac medication before pregnancy ($P < 0.0001$), and left heart obstruction ($P < 0.0001$). New characteristics were mechanical valve replacement ($P = 0.0014$), and systemic ($P = 0.04$) or pulmonary atrioventricular valve regurgitation related with the underlying (moderately) complex CHD ($P = 0.03$). A new risk score for cardiac complications is proposed. The most prevalent obstetric complications were hypertensive complications (12.2%). No correlation of maternal characteristics with adverse obstetric outcome was found. The most prevalent neonatal complications were premature birth (12%), small for gestational age (14%), and mortality (4%). Cyanotic heart disease (corrected/uncorrected) ($P = 0.0003$), mechanical valve replacement ($P = 0.03$), maternal smoking ($P = 0.007$), multiple gestation ($P = 0.0014$), and the use of cardiac medication ($P = 0.0009$) correlated with adverse neonatal outcome.

**Conclusion** In our tertiary CHD cohort, cardiac, obstetric, and neonatal complications were frequently encountered, and (new) correlations of maternal baseline data with adverse outcome are reported. A new risk score for adverse cardiac complications is proposed, although prospective validation remains necessary.

**Keywords** Congenital heart disease • Pregnancy • Complications

## Introduction

Progress in the fields of diagnostic techniques and surgical intervention has dramatically improved long-term outcome in patients with congenital heart disease (CHD). As a consequence, most patients with congenital cardiac malformations reach childbearing age. Many of these women wish to become pregnant. Pregnancy itself is a circulatory burden, primarily due to volume loading, which has an impact even on a healthy woman's life. In the face of residual lesions or sequelae after correction or an uncorrected maternal congenital heart defect, this burden may have deleterious effects on the health of both the mother and her offspring. Cardiac, obstetric, and neonatal complications all appear to be more prevalent.[1]

It has long been recognized that certain cardiac factors, including pre-pregnancy NYHA class, the presence of a mechanical valve prosthesis, having pulmonary hypertension/cyanosis, and outflow tract obstruction, adversely influences pregnancy outcome. The

* Corresponding author. Tel: +31 50 361 5288, Fax: +31 50 361 4391, Email: w.drenthen@thorax.umcg.nl

'CARdiac disease in PREGnancy' (CARPREG) investigators were the first to identify predictors of the adverse pregnancy outcome in women with established heart disease. The investigators also were the first to design a risk score, which is now commonly used to 'predict' cardiac complications during pregnancy in the context of maternal CHD. Limitations of the score for patients with CHD are that it is developed based on a cohort that included patients with primary electrical disease as well as acquired heart disease. Moreover, several types of (mainly complex) CHD were underrepresented.[2,3] It is suggested that the CARPREG cardiac risk score therefore needs to be modified to assess the risk of pregnancy in women with CHD.[4]

The primary objective of the present study is to identify patient characteristics associated with adverse pregnancy outcome in a patient cohort consisting of patients with CHD and to propose a modified risk score.

# Methods

For the present ZAHARA study, female patients with CHD aged 18–58 years enrolled in the nation-wide CONgenital CORvitia (CONCOR) registry and a Belgian tertiary medical centre's adult CHD database were identified. The databases include patients with CHD >18 years receiving tertiary medical care. The institutional review board or Ethics Committee at each of the seven participating tertiary centres approved the protocol. Patients alive at the time of inclusion (survivors) were contacted by mail and asked to provide written informed consent. The Ethics Committee did not allow review of medical charts without consent. Moreover, we were not allowed to contact family members of deceased patients to retrieve informed consent. Therefore, no information on excluded or deceased patients is available.

Data were retrospectively obtained from medical records as reported by qualified medical personnel and supplemented data were retrieved by a telephonic questionnaire. The questionnaire was mainly used to check data concerning the date of birth/death of offspring, birth weight as recorded in official birth certificates, and to check whether or not external (non-tertiary) medical personnel was consulted to obtain complete data concerning each pregnancy.

Baseline data including maternal date of birth, parity, age at pregnancy when applicable, basic anatomy, prior surgical procedures, co-morbidity, and medical history (using the European Paediatric Cardiac Coding) were recorded for all women who gave informed consent. Miscarriages and elective abortions were excluded as data concerning these pregnancies are often disputable and unreliable. Besides the baseline data, the following complications were recorded for each completed (>20 weeks of gestation) pregnancy between 1980 and 2007. *Cardiac complications* (as diagnosed by a tertiary care cardiologist specialist): clinically significant ('requiring treatment at least including drug prescription') episodes of arrhythmia or heart failure, cardiovascular complications (e.g. thrombo-embolic complications, myocardial infarction, and/or cerebrovascular accidents), and endocarditis (including first 6 months post-partum). *Obstetric complications*: pregnancy-induced hypertension (PIH, new onset hypertension: blood pressure >140 mmHg systolic or >90 mmHg diastolic without proteinuria after 20 weeks of gestation); preeclampsia (PIH with >0.3 g protein in 24 h urine sample); eclampsia (preeclampsia with grand mal seizures); haemolysis elevated liver enzymes low platelets (HELLP) syndrome according to the guidelines of the European Society of Gynaecology and Obstetrics; premature labour (<37 weeks of gestation); post-partum haemorrhage (vaginal delivery >500 mL, caesarean section >1000 mL). *Neonatal outcome*: premature delivery (delivery <37 weeks); small-for-gestational-age birth weight (<10th percentile); offspring mortality [demise: *in utero* (>20 weeks of gestation)—the first-year post-partum].

## Data analysis

A Clintrial data-entry program was used to record information and converted to SPSS (version 16.0) and SAS for statistical analysis. Descriptive statistics for nominal data were expressed in absolute numbers and percentages. Mean values and standard deviations were presented for normally distributed continuous variables. For non-normal distributed continuous variables, median and ranges were computed. Univariable logistic regression analysis was performed to identify patient characteristics associated with adverse pregnancy outcome divided into three composite endpoints (as defined above): the cardiac, obstetric complications, and offspring outcome. The following baseline variables were assessed: the presence of patent shunt [atrial septal defect, ventricular septal defect (VSD), persistent ductus arteriosus, and abnormal pulmonary vein connections], surgical status prior to pregnancy (palliation, corrected or uncorrected), history of arrhythmias or cardiac complications (heart failure, cerebrovascular accidents, transient ischaemic attack, myocardial infarction, thrombo-embolic complications, and endocarditis), left heart obstruction [(i) peak aortic gradient >30 mmHg or aortic valve area <1.5 $cm^2$ or mitral valve area <2 $cm^2$ [2] and (ii) peak aortic gradient >50 mmHg or aortic valve area <1.0 $cm^2$], right ventricular outflow tract obstruction >50 mmHg, reduced systemic ventricular function (qualitative ejection fraction or graded quantitative ejection fraction <40% based on echocardiography), presence of cyanosis (oxygen saturation <90%) or pulmonary hypertension (systolic pulmonary artery pressure >50 mm Hg),[2] pulmonary valve regurgitation (moderate or severe), systemic valve regurgitation (moderate or severe), pulmonary atrioventricular (AV) valve regurgitation (moderate or severe), systemic AV valve regurgitation (moderate or severe), aortic dilatation >40 mm (widest diameter), the presence of a mechanical valve prosthesis, the presence of a pacemaker, twin pregnancy, cyanotic heart disease (corrected/uncorrected): CHD which presents at or shortly after birth with cyanosis regardless of subsequent performed palliative corrective interventions, smoking immediately prior to or during pregnancy, alcohol during pregnancy (>0 U/day on average), use of oral anticoagulation and/or other cardiovascular medication during pregnancy, and maternal NYHA class prior to pregnancy. Variables that were associated with an increased incidence of the studied endpoints ($P < 0.15$) entered the multivariable stage. The final multivariable model was then constructed by backward deletion of the least significant characteristic, until all remaining variables were significantly ($P < 0.05$) associated with the endpoint. Because some women underwent one or more pregnancies, the validity of treating each pregnancy as an independent event was determined by general estimating equation analysis.

For each pregnancy, the now widely used CARPREG cardiac risk score was calculated.[2] We subsequently validated this score for the abovementioned combined endpoint cardiac complications. We calculated the *C*-index (concordance index) of the CARPREG risk score, which describes the discriminative capacity, and performed a calibration using the Hosmer–Lemeshow test. The *C*-index has a value between 0.5 (poor discrimination) and 1.0 (perfect discrimination). We then modified the CARPREG risk score using the identified multivariable associations for the composite cardiac endpoint, nevertheless retaining the basic principal of this risk score.[2] In the modified risk score, we use the exponent value to weigh the risk factors and

**Table 1 Complications found during 1302 completed pregnancies organized per category of congenital heart disease**

| Congenital heart disease | N | Cardiac complications | | | | Obstetric complications | | | | | | Neonatal complications | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | AR | HF | CE | EN | PI | PE | EC | HE | PL | PH | PD | SG | MO |
| Atrial septal defect | 188 | 7 | 0 | 2 | 0 | 9 | 12 | 0 | 0 | 12 | 19 | 12 | 33 | 4 |
| Aortic coarctation | 160 | 2 | 1 | 0 | 1 | 8 | 7 | 0 | 0 | 8 | 19 | 22 | 18 | 6 |
| Ventricular septal defect | 148 | 1 | 0 | 1 | 1 | 8 | 9 | 0 | 0 | 7 | 16 | 6 | 16 | 1 |
| Pulmonary valve stenosis | 148 | 3 | 1 | 3 | 0 | 12 | 7 | 2 | 1 | 5 | 16 | 20 | 15 | 7 |
| Tetralogy of Fallot | 124 | 7 | 1 | 1 | 0 | 5 | 4 | 0 | 0 | 9 | 12 | 21 | 20 | 7 |
| Marfan syndrome | 118 | 1 | 0 | 2 | 0 | 13 | 1 | 0 | 0 | 5 | 11 | 16 | 14 | 8 |
| Atrioventricular septal defects | 89 | 15 | 3 | 2 | 0 | 9 | 2 | 0 | 0 | 6 | 12 | 10 | 15 | 4 |
| Aortic valvar stenosis | 81 | 3 | 4 | 0 | 0 | 10 | 3 | 1 | 1 | 5 | 5 | 10 | 9 | 1 |
| Complete transposition of the great arteries | 52 | 11 | 4 | 2 | 0 | 7 | 5 | 0 | 1 | 6 | 7 | 16 | 10 | 5 |
| Ebstein malformation | 22 | 2 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 4 | 2 | 1 | 1 |
| Congenital corr. transposition of great arteries | 19 | 1 | 2 | 0 | 0 | 2 | 0 | 0 | 2 | 1 | 1 | 1 | 3 | 0 |
| Pulmonary atresia | 12 | 3 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 1 | 1 | 0 |
| Pulmonary hypertension or Eisenmenger[a] | 4 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 |
| Complex cyanotic heart disease | 9 | 3 | 2 | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 2 | 6 | 5 | 1 |
| Other | 128 | 3 | 2 | 3 | 0 | 10 | 7 | 0 | 0 | 11 | 15 | 15 | 20 | 4 |
| Overall | 1302 | 62 | 21 | 17 | 2 | 94 | 57 | 4 | 6 | 76 | 139 | 160 | 180 | 49 |

*N*, number of pregnancies. AR, arrhythmias; HF, heart failure; CE, cardiovascular complications; EN, endocarditis; PI, pregnancy-induced hypertension; PE, preeclampsia; EC, eclampsia; HE, HELLP syndrome; PL, premature labour; PH, post-partum haemorrhage; PD, premature delivery; SG, small for gestational age; MO, foetal or neonatal mortality.
[a]Respectively, ASD related $n = 2$ and VSD related $n = 2$.

attribute points per risk factor. The developed risk model based on the whole study cohort was further evaluated by drawing 1000 bootstrap samples, with replacement, to estimate the extent to which the predictive accuracy of the model was overoptimistic. We report the mean *C*-index and the corresponding standard error (SEM).

# Results

Overall, 1802 women with CHD (82%) provided written informed consent to review their medical records. These patients had 1696 gestations, including 336 miscarriages (19.4%; <20 weeks of gestation) and 58 elective abortions (3.4%). For the present analyses, the data of the 1302 completed pregnancies in 714 individual women were used. Most patients were nulliparous (63%). Mean maternal age at pregnancy was 27.4 (SD ± 2.6) years. The underlying CHD in the women with completed (>20 weeks of gestation) pregnancies in detail: (un)-corrected atrial septal defect II ($n = 188$), (un)-corrected aortic coarctation including additional cardiac defects ($n = 160$), (un)-corrected VSDs ($n = 148$), pulmonary valve stenosis ($n = 148$; including 21 with >50 mmHg obstruction), corrected Tetralogy of Fallot ($n = 124$), Marfan syndrome ($n = 118$; including 32 with aortic root dilatation >40 mm), atrioventricular septal defect ($n = 89$, of which 15 with common orifice), aortic valvar stenosis ($n = 81$, including 18 with >50 mmHg obstruction), atrial or arterial corrected complete transposition of great arteries (TGA) ($n = 52$, mostly Mustard corrections), (un)-corrected Ebstein malformations ($n = 22$), congenital corrected TGA ($n = 19$), pulmonary atresia with VSD ($n = 12$), Eisenmenger syndrome ($n = 4$), complex cyanotic heart disease ($n = 9$, including patients with Fontan palliation), and other CHD [$n = 128$, including isolated mitral/tricuspid valvar regurgitation (respectively, $n = 30$ and $n = 1$)]. The distribution of complications encountered during these completed (>20 weeks of gestation) pregnancies is illustrated in *Table 1*. It needs to be stated that, in part, these results are published in the earlier work by our research group and are merely shown for illustrative purposes.[5–14] Main cardiac complications were arrhythmias (4.7%) and heart failure (1.6%), mostly transient in nature and manageable with medical therapy. The most important obstetric complications were hypertension-related disorders (mainly occurring in uncorrected patients). The most frequently encountered offspring outcomes were born small for gestational age and premature delivery. Maternal cardiac complications and offspring complications were highly correlated ($r = 0.85$, $P = 0.002$).

The results of the univariable logistic regression are shown in *Table 2*. The event rate per characteristic is reported in *Table 3*. The multivariate model correlating the composite endpoints of cardiac and neonatal complications is shown in *Table 4*. New independent (multivariable) factors associated with cardiac complications were the presence of a moderate-to-severe pulmonary or systemic AV valve regurgitation, cyanotic heart disease (corrected/uncorrected), and the presence of mechanical valve prosthesis. A history of arrhythmias, maternal NYHA functional class, the presence of left ventricular outflow tract obstruction, and the use of cardiac drugs also proved to be independent predictors of cardiac complications in concordance with previous studies. None of the investigated patient characteristics were associated with adverse obstetric complications. The presence of multiple gestations, the presence of at birth cyanotic heart disease, the presence of mechanical valve prosthesis, smoking during pregnancy, and the use of

**Table 2 Results of univariable logistic regression for the composite endpoints: cardiac, obstetric, and offspring complications**

| | Cardiac complications | Obstetric complications | Neonatal complications |
|---|---|---|---|
| Patent shunt | 0.6 (0.3–1.0) | 1.0 (0.7–1.3) | 0.7 (0.5–1.0) |
| Only palliation before pregnancy | **9.8 (2.8–34.1)*** ** | 1.7 (0.4–7.1) | 2.7 (0.7–10.9) |
| Corrected before pregnancy | 1.6 (1.0–2.7) | 1.0 (0.8–1.4) | 1.3 (1.0–1.7) |
| History of arrhythmias | **5.0 (2.3–11.0)*** ** | 0.9 (0.3–2.3) | 1.2 (0.6–2.6) |
| History of cardiac complications | 1.5 (0.4–5.0) | 1.0 (0.4–2.3) | **2.2 (1.0–4.7)*** |
| LHO (PG >30 mmHg or AVA <1.5 $cm^2$) + mitral valve stenosis (MVA <2.0 $cm^2$)[a] | **2.6 (1.2–5.5)*** | 1.0 (0.5–1.8) | **0.5 (0.3–0.9)*** |
| LHO (PG >50 mmHg or AVA <1.0 $cm^2$) | **7.4 (2.6–21.2)*** ** | 0.4 (0.1–1.5) | 0.6 (0.2–1.6) |
| Pulmonary ventricular outflow obstruction (PG >50 mmHg) | 2.2 (0.9–5.7) | 1.4 (0.7–2.5) | 1.2 (0.7–2.1) |
| Reduced systemic ventricular function | **3.3 (1.3–8.3)**** | 0.5 (0.2–1.2) | 1.6 (0.7–3.7) |
| Cyanosis or pulmonary hypertension | 1.9 (0.3–12.9) | 0.6 (0.1–3.9) | 3.2 (0.8–12.9) |
| Pulmonary valve regurgitation (moderate/severe) | 1.5 (0.7–3.5) | 1.2 (0.8–2.0) | 0.9 (0.5–1.4) |
| Systemic valve regurgitation (moderate/severe) | 1.1 (0.4–2.9) | 1.0 (0.5–1.7) | 0.8 (0.4–1.5) |
| Systemic AV valve regurgitation (moderate/severe) | **2.7 (1.4–5.2)**** | 0.9 (0.6–1.5) | 1.4 (0.8–2.2) |
| Pulmonary AV valve regurgitation (moderate/severe) | **2.9 (1.6–5.4)*** ** | 0.8 (0.5–1.3) | 1.4 (0.8–2.1) |
| Aortic dilatation (>40 mm) | 1.7 (0.7–4.5) | 0.8 (0.4–1.7) | 0.8 (0.4–1.6) |
| Mechanical prosthesis | **37.1 (3.8–360.8)**** | 9.3 (1.0–90.1) | 9.0 (0.9–87.3) |
| Pacemaker | **4.6 (1.8–11.5)**** | **2.7 (1.1–6.6)**** | 0.5 (0.2–1.5) |
| Twin or multiple gestation | 2.0 (0.6–7.0) | 2.3 (1.0–5.9) | **6.4 (2.3–17.8)*** ** |
| Cyanotic heart disease (corrected and uncorrected) | **2.8 (1.7–4.7)*** ** | 0.9 (0.6–1.3) | **2.0 (1.4–2.9)*** ** |
| Smoking before pregnancy | 0.9 (0.5–1.5) | 0.9 (0.6–1.2) | 1.4 (1.0–1.9) |
| Smoking during pregnancy | 1.1 (0.6–2.0) | 0.7 (0.4–1.0) | **1.6 (1.1–2.3)**** |
| Alcohol during pregnancy | 1.2 (0.6–2.6) | 1.2 (0.7–2.0) | 0.7 (0.4–1.2) |
| Oral anticoagulation | **5.7 (2.4–13.5)*** ** | 1.9 (0.8–4.7) | 2.7 (1.0–7.2) |
| Other cardiac medication before pregnancy | **4.2 (2.3–7.8)*** ** | 1.0 (0.6–1.8) | **2.1 (1.4–3.3)*** ** |
| NYHA | **3.1 (1.6–6.0)*** ** | 0.8 (0.4–1.4) | 1.1 (0.7–1.8) |

AV, atrioventricular; AVA, aortic valve area; LHO, left heart obstruction; MVA, mitral valve area; NYHA, New York Heart Association; PG, peak gradient; Pulm, pulmonary; Syst, systemic. Values are expressed as odds ratio (95% CI).
[a]None of the patients had an MVA of <2.0 $cm^2$.
*$P < 0.05$.
**$P < 0.01$.
***$P < 0.001$.
The bold entries are the statistical significant data, which makes interpretation simpler.

cardiac medication other than anticoagulation regimes were independently associated with adverse neonatal complications. In *Table 5*, the details regarding the encountered cardiac complications are described, including the underlying CHD. The performance of the CARPREG cardiac risk score was limited with a *C*-index of 0.656 for the composite cardiac endpoint. *Figure 1* shows the alternative risk score and the corresponding cardiac risk during pregnancy. The mean *C*-index of this risk model, as obtained in the 1000 bootstrap samples, was 0.762 with an SEM of 0.026. This implies some over-optimism in the estimated predictive accuracy of the model. In the future, this new cardiac risk index needs to be externally validated in a prospective study.

# Discussion

The present, and thus far largest, study investigates the pregnancy complications in women with CHD. Complications were frequently encountered. Several new associations with adverse cardiac and neonatal pregnancy complications were identified. On the basis of these associations, a new risk index was designed, which seems to enhance discrimination and calibration compared with the existing CARPREG risk score. External validation of this risk score in a large prospective study, however, remains necessary.

## Predicting cardiac complications

In our study, cardiac complications occurred during 7.6% of completed pregnancies, slightly lower than the 11% reported in our recent review.[1] Clinically significant episodes of arrhythmias (4.7%) and heart failure (1.6%) were the most important of cardiac complications. The lower prevalence of cardiac complications was largely attributable to the lower incidence of heart failure (1.6 vs. 4.8%).[1] As heart failure is difficult to distinguish from 'normal' physiological developments associated with pregnancy, including malleolar oedema, shortness of breath during

**Table 3 Event rate per characteristics in absolute numbers (percentages) for the three composite endpoints: cardiac, obstetric, and offspring complications**

| | *N* | Cardiac complications, *n* (%) | Obstetric complications, *n* (%) | Neonatal complications, *n* (%) |
|---|---|---|---|---|
| Overall | 1302 | 99 (7.6) | 313 (24.0) | 331 (25.4) |
| Patent shunt | 306 | 14 (4.6) | 72 (23.5) | 65 (21.2) |
| Only palliation before pregnancy | 9 | **4 (44.4)** | 3 (33.3) | 4 (44.4) |
| Corrected before pregnancy | 683 | 65 (9.5) | 166 (24.3) | 189 (27.7) |
| History of arrhythmias | 39 | **12 (30.8)** | 9 (23.1) | 12 (30.8) |
| History of cardiac complications | 33 | 3 (9.1) | 7 (21.2) | **13 (39.4)** |
| LHO (PG >30 mmHg or AVA <1.5 $cm^2$) + mitral valve stenosis (MVA < 2.0 $cm^2$)[a] | 71 | **11 (15.5)** | 16 (22.5) | **11 (15.5)** |
| LHO (PG >50 mmHg or AVA <1.0 $cm^2$) | 22 | **7 (31.8)** | 2 (9.1) | 4 (18.2) |
| Pulmonary ventricular outflow obstruction (PG >50 mmHg) | 68 | 10 (14.7) | 21 (30.9) | 20 (29.4) |
| Established reduced systemic ventricular function | 35 | **7 (20.0)** | 5 (14.3) | 14 (40.0) |
| Cyanosis or pulmonary hypertension | 9 | 1 (11.1) | 1 (11.1) | 5 (55.6) |
| Pulmonary valve regurgitation (moderate/severe) | 109 | 11 (10.1) | 29 (26.6) | 24 (22.0) |
| Systemic valve regurgitation (moderate/severe) | 76 | 6 (7.9) | 16 (21.1) | 16 (21.1) |
| Systemic AV valve regurgitation (moderate/severe) | 106 | **17 (16.0)** | 24 (22.6) | 34 (32.1) |
| Pulmonary AV valve regurgitation (moderate/severe) | 105 | **18 (17.1)** | 21 (20.0) | 33 (31.4) |
| Aortic dilatation (>40 mm) | 58 | 6 (10.3) | 13 (22.4) | 12 (20.7) |
| Mechanical prosthesis | 4 | **4 (100.0)** | 3 (75.0) | 3 (75.0) |
| Pacemaker | 29 | **8 (27.6)** | **14 (48.3)** | 4 (13.8) |
| Twin or multiple gestation | 17 | 2 (11.8) | 7 (41.2) | **11 (64.7)** |
| Cyanotic heart disease (corrected and uncorrected) | 198 | **31 (15.7)** | 45 (22.7) | **75 (37.9)** |
| Smoking before pregnancy | 313 | 21 (6.7) | 70 (22.4) | 96 (30.7) |
| Smoking during pregnancy | 192 | 14 (7.3) | 34 (17.7) | **66 (34.4)** |
| Alcohol during pregnancy | 89 | 7 (7.9) | 22 (24.7) | 16 (18.0) |
| Oral anticoagulation | 24 | **10 (41.7)** | 10 (41.7) | 12 (50.0) |
| Other cardiac medication before pregnancy | 96 | **21 (26.2)** | 21 (26.2) | **34 (42.5)** |

AV, atrioventricular; AVA, aortic valve area; LHO, Left heart obstruction; MVA, mitral valve area; NYHA, New York Heart Association; PG, peak gradient; Pulm, pulmonary; Syst, systemic.
[a]None of the patients had an MVA of <2.0 $cm^2$.
The bold entries are the statistical significant data, which makes interpretation simpler.

exercise, and increased nocturnal urination frequency, we used a strict definition. The occurrences of other cardiac complications were in line with expectations.

New associations with adverse cardiac complications were: (i) the presence of moderate of severe systemic or pulmonary AV valve regurgitation, (ii) the presence of mechanical valve prosthesis, and (iii) 'at birth' cyanotic CHD. (i) The presence of significant AV valve regurgitation is known to cause volume loading and atrial distension. These factors are subsequently linked with the development of heart failure and supraventricular arrhythmias. In patients with significant pulmonary AV valve regurgitation, the majority of complications were arrhythmias. The vulnerability to develop arrhythmias is a well-known long-term complication in these patients even outside pregnancy. Up till now, due to the decrease in systemic vascular resistance, the importance of systemic AV valve regurgitation during pregnancy was thought to be limited. Therefore, our finding that moderate/severe systemic AV valve regurgitation independently predicts maternal complications is important, in particular as half of the complications consisted of heart failure. Importantly, we need to realize that in a significant proportion of patients, the moderate–to-severe AV valve regurgitation was associated with (moderately) complex CHD, and concomitant ventricular dysfunction and/or dilatation may have been involved in the development of complications. This risk factor should therefore be interpreted in the context of the associated heart disease and ventricular function. (ii) The fact that the presence of a mechanical valve correlated with adverse cardiac outcome is not surprising. Several case series and reports have described important cardiac complications including maternal mortality, heart failure, arrhythmias, and mechanical valve thrombosis.[15–17] Especially, although not exclusively, patients with old generation valves in mitral valve position appeared at greater risk for valve thrombosis.[15] In all our patients with mechanical valves, cardiac complications occurred (*Table 4*), including mechanical valve thrombosis during two pregnancies, one in a woman with a high-risk mechanical prosthesis (mitral Björk Shiley) but the

**Table 4 Multivariable model for the composite endpoints of cardiac and neonatal complications corrected for maternal age and parity**

| | Odds ratio (95% CI) | *P*-value |
|---|---|---|
| Cardiac complications | | |
| History of arrhythmias | 4.3 (1.8–10.2) | 0.0011 |
| Other cardiac medication before pregnancy | 4.2 (2.1–8.6) | <0.0001 |
| NYHA functional class | 2.2 (1.1–4.5) | 0.0298 |
| LHO (PG >50 mmHg or AVA <1.0 $cm^2$) | 12.9 (3.9–42.3) | <0.0001 |
| Syst AV valve regurgitation (moderate/severe) | 2.0 (1.0–4.0) | 0.0427 |
| Pulm AV valve regurgitation (moderate/severe) | 2.3 (1.1–5.0) | 0.0287 |
| Mechanical valve prosthesis | 74.7 (5.3–1057) | 0.0014 |
| Cyanotic heart disease (corrected and uncorrected) | 3.0 (1.7–5.0) | <0.0001 |
| Neonatal complications | | |
| Twin or multiple gestation | 5.4 (1.9–15.2) | 0.0014 |
| Smoking during pregnancy | 1.7 (1.2–2.4) | 0.0070 |
| Cyanotic heart disease (corrected and uncorrected) | 2.0 (1.4–2.9) | 0.0003 |
| Mechanical valve prosthesis | 13.9 (1.2–157) | 0.0331 |
| Other cardiac medication before pregnancy | 2.2 (1.4–3.5) | 0.0009 |

AV, atrioventricular; AVA, aortic valve area; LHO, left heart obstruction; NYHA, New York Heart Association; PG, peak gradient; Pulm, pulmonary; Syst, systemic.

other in a woman with a bileaflet aortic valve. Both events presented shortly after switching therapy from subcutaneous full fixed dose low molecular weight heparin to oral anticoagulation consisting of acenocoumarol. At present, the anticoagulation regime best used during pregnancy in women with mechanical valves is still a subject of debate. The used schedule is not advocated in the official ESC guideline.[18] Moreover, in our patients, anti-factor Xa levels were not monitored; this may well have negatively affected the occurrence of valve thrombosis. (iii) The fact that patients with at birth cyanotic heart disease appear to be at greater risk for cardiac complications most likely reflects the complexity of the underlying heart condition. Patients with more complex heart disease need more interventions and are more prone to develop complications outside pregnancy.[19] The burden of pregnancy may accelerate the development of adverse cardiac complications.

In concordance with the CARPREG and other investigators, we identified NYHA functional class >II, left heart obstructive lesions, and a history of arrhythmias to be independent predictors of maternal cardiac complications.[20,21] It needs to be added that arrhythmias were the most common cardiac complication in women with a history of arrhythmias. Silversides *et al.*[22] reported earlier that in women with pre-existing cardiac rhythm disorders, exacerbation of arrhythmic episodes during pregnancy was common.

In contrast to the CARPREG report, a decreased systemic ventricular function was a univariate but not multivariate predictor of cardiac complications. In this retrospective study, we had to use a less accurate definition for decreased left ventricular function (subjective mostly echocardiographic estimation vs. measurement of ejection fraction in the CARPREG study) which may in part explain this difference. The association between significant systemic AV valve regurgitation and decreased systemic ventricular function (e.g. in patients with a systemic right ventricle) may be another part of the explanation, as systemic AV valve regurgitation emerged as an independently associated characteristic in our study. Cyanosis and a history of cardiac complications also did not correlate with adverse cardiac outcome. The low incidence of these variables may at least be in part the explanation. Cyanotic women are often advised against pregnancy.[23]

## Predicting obstetric complications

Obstetric complications were observed during 24% of completed pregnancies. Hypertensive disorders of pregnancy were the most important obstetric complication occurring in 12.2% (including preeclampsia in 4.4%). No plausible associations with adverse obstetric outcome were found.

## Predicting neonatal complications

Neonatal complications were premature birth (12%), small for gestational age (14%), and mortality (4%), overall complicating 25% of completed pregnancies. In comparison with the results summarized in our literature review, the occurrence of small for gestational age and offspring mortality is higher, which could be mainly attributed to the relatively higher percentage of complex CHD.

New associations were the use of cardiac medication, 'at birth' cyanotic heart disease, and mechanical valve prosthesis. The fact that at birth cyanotic heart disease and the use of cardiac medication predicted neonatal complications most probably reflects the severity of the underlying heart disease. Mechanical valve prosthesis mainly resulted in premature delivery which may be the result of precautions taken by the attending physician as most deliveries were induced prematurely (possibly because of maternal cardiac complications). In several case series, similar observations were done.[16,17]

In the CARPREG study, predictors for neonatal complications were NYHA functional class or cyanosis, left heart obstructive lesions, smoking during pregnancy, multiple gestations, and the use of anticoagulation during pregnancy. In our population, the maternal functional class >II or cyanosis did not appear to be a risk factor, probably at least in part due to the low prevalence in our population. Also patients with left heart obstruction did not appear to be at greater risk for offspring complications. In correspondence with the report by Siu *et al.*, in our study, women with a twin gestation and those who smoke during pregnancy were at a higher risk for offspring complications (*Table 5*). The most important risk associated with multiple gestations is spontaneous preterm delivery, which is subsequently related with increased perinatal mortality and morbidity.[24,25] Smoking during pregnancy is also a well-known risk factor that affects neonatal outcome.[26]

**Table 5** Presence of predictors and the number of complications encountered in these patients

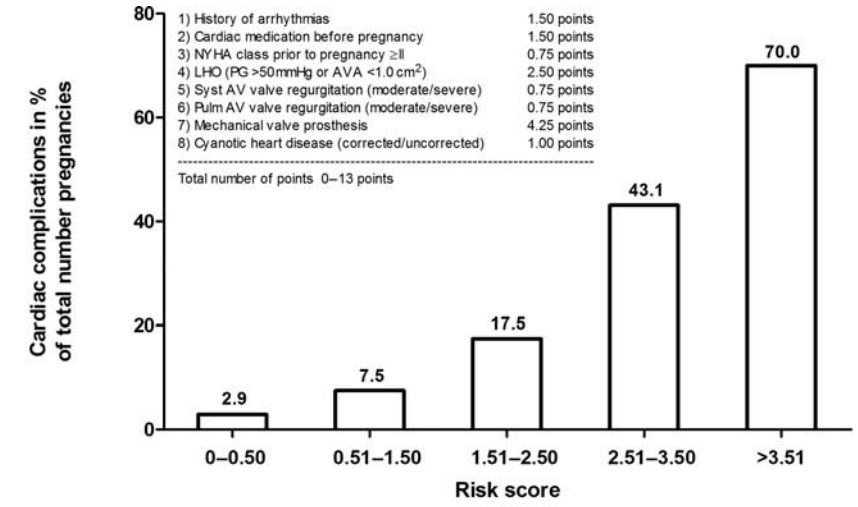
| Risk factor | N | Cardiac complications | Underlying CHD in pregnancies with complications |
|---|---|---|---|
| History of arrhythmias | 39 | AR ($n = 8$); HF ($n = 1$); CE ($n = 3$); EN ($n = 0$) | TGA 3; ASD 2; ccTGA 1; AOS 1; TOF 1; VSD 1; AVSD 1; PS 1; UVH 1 |
| Other cardiac medication before pregnancy | 80 | AR ($n = 16$); HF ($n = 4$); CE ($n = 4$); EN ($n = 0$) | TGA 6; AVSD 5; TOF 3; Marfan 2; MR 1, AOR 1; VSD 1; ASD 1 |
| NYHA functional class | 7 | AR ($n = 1$); HF ($n = 1$); CE ($n = 0$); EN ($n = 0$) | PAVSD 1; AOR 1 |
| LHO (PG >50 mmHg or AVA <1.0 $cm^2$) | 22 | AR ($n = 2$); HF ($n = 2$); CE ($n = 0$); EN ($n = 0$) | AOS 5; AVSD 1; CoA 1 |
| Syst AV valve regurgitation (moderate/ severe) | 106 | AR ($n = 7$); HF ($n = 8$); CE ($n = 1$); EN ($n = 0$) | AVSD 9; TGA 3; ccTGA 1; MVP 1; AOS 1; Eisenmenger 1 |
| Pulm AV valve regurgitation (moderate/ severe) | 105 | AR ($n = 10$); HF ($n = 3$); CE ($n = 2$); EN ($n = 1$) | AVSD 6; Ebstein 3; PAVSD 3; DORV 1; TOF 1; VSD 1; Eisenmenger 1 |
| Mechanical valve prosthesis[a] | 6 | AR ($n = 3$); HF ($n = 2$); CE ($n = 2$);[b] EN ($n = 0$) | AOS 3; AOR 1; MR 2 |
| Cyanotic heart disease (corrected and uncorrected) | 198 | AR ($n = 24$); HF ($n = 8$); CE ($n = 3$); EN ($n = 0$) | TGA 13; TOF 9; PAVSD 3; UVH 3; DORV 1; AOS 1; Eisenmenger 1 |
| | | **Neonatal complications** | |
| Twin or multiple gestation | 18 | PD ($n = 10$); SG ($n = 4$); MO ($n = 1$) | |
| Smoking during pregnancy | 192 | PD ($n = 28$); SG ($n = 40$); MO ($n = 8$) | |
| Cyanotic heart disease (corrected and uncorrected) | 198 | PD ($n = 46$); SG ($n = 34$); MO ($n = 13$) | |
| Mechanical valve prosthesis[c] | 6 | PD ($n = 3$); SG ($n = 1$); MO ($n = 0$) | |
| Other cardiac medication before pregnancy | 80 | PD ($n = 22$); SG ($n = 14$); MO ($n = 7$) | |

AOR, aortic valve regurgitation; AOS, aortic valve stenosis; AR, arrhythmias; ASD, atrial septal defect; AV, atrioventricular; AVA, aortic valve area; AVSD, atrioventricular septal defect; ccTGA, congenital corrected transposition of great arteries; CE, cardiovascular complications; CoA, aortic coarctation; DORV, double outlet right ventricle; EN, endocarditis; HF, heart failure; LH, left heart; Marfan, Marfan syndrome; MO, foetal or neonatal mortality; MR, isolated mitral valve regurgitation; MVP, mitral valve prolaps; NYHA, New York Heart Association; PAVSD, pulmonary atresia with VSD; PD, premature delivery; PG, peak gradient; PS, pulmonary valve stenosis; Pulm, pulmonary; SG, small for gestational age; Syst, systemic; TGA, atrial complete transposition of great arteries; TOF, Tetralogy of Fallot; UVH, univentricular heart; VSD, ventricular septal defect.

[a]Position of mechanical valve: 4 aortic, 2 mitral; type of mechanical valve: all bileaflet, except 1 Bjork-Shiley mitral valve.

[b]Both cardiovascular complications were mechanical valve thromboses occurring at 12 and 14 weeks of gestation shortly after switch of full dose subcutaneous low molecular weight heparin back to oral anticoagulation (one aortic bileaflet prosthesis; one Björk shiley mitral valve prosthesis). No other risk factors for thrombotic complications were present during these pregnancies. One of these patients had two additional episodes of thrombosis during the same pregnancy, which were not analysed separately.

[c]Including the two pregnancies complicated by mechanical valve thrombosis.




| | | | | | |
|---|---|---|---|---|---|
| Number of pregnancies at risk | 828 | 280 | 126 | 58 | 10 |
| Percentage of total population | 63.6 | 28.1 | 6.1 | 1.4 | 0.8 |

**Figure 1** The modified risk score for cardiac complications during completed (>20 weeks of gestation) pregnancies in women with congenital heart disease (expressed as % of the total number of completed pregnancies). AV, atrioventricular; AVA, aortic valve area; LHO, left heart obstruction; NYHA, New York Heart Association; PG, peak gradient; Pulm, pulmonary; Syst, systemic.

## Risk scores

The CARPREG risk score performed inadequately in our population and largely overestimated risk, in line with other reports.[27,28] The differences between the populations that we pointed out may in part explain the poor performance of the CARPREG cardiac risk score in our population. In addition, the incidence of cardiac complications appears relatively low (7.6%) in comparison to 13 and 19.4% reported by Siu *et al.*[2,3,29] and Khairy *et al.*[4] However, the cardiac complication rate in the CARPREG study in patients with CHD is 7.1% (32 in 445 pregnancies). Apparently, acquired or arrhythmic heart disease patients are at higher risk. The cohort investigated by Khairy *et al.* had an overrepresentation of complex CHD, which may explain the higher cardiac complication rate. Nonetheless, the different definition of heart failure (therapeutic interventions had to be performed) that we needed to use in this retrospective study could also in part explain this discrepancy. The incidence of cardiac complications in our study, however, is comparable to the frequency found in a recently published literature review.[1] The modification of the risk index (as explained in the Results section) seems to enhance discrimination and calibration. Importantly, both risk scores have significant limitations restricting indiscriminative use. The representation of risk factors in the population determines which risk factors emerge. Important risk factors such as pulmonary arterial hypertension are likely to be underrepresented in contemporaneous cohorts, preventing such risk factors to be identified. Therefore, it is important to underline that the calculation of risk scores should be only a part of pre-pregnancy risk assessment. We advocate a pre-pregnancy evaluation in an outpatient setting, including physical examination, laboratory evaluation, and an echocardiography according to a predefined protocol by an expert in the field. In addition to weighing predictors found in ZAHARA and CARPREG and calculating risk scores, disease-specific information should always be used when estimating pregnancy risk in order to avoid over-simplification implied by risk calculation. Also existing guidelines and expert articles should be consulted.[30] External validation of our modified risk score in a large prospective study remains necessary, before use in everyday practice is possible.

## Limitations

Most of the limitations of the present study are related to the retrospective design. First and most importantly, the present study lacks a historical 'matching' control population. This is, however, not as straightforward and simple exercise, as the vast majority of healthy women in the Netherlands and Belgium deliver at home with the help of a midwife. Therefore, the women consulting gynaecological hospital care are a selected population with (mainly obstetric or neonatal) complications or at higher risk for these complications. Moreover, the concept of a control population is, in our opinion, only sustainable, when both cohorts are followed in an identical fashion according to a predefined protocol. Therefore, a prospective study would be the best option, on the other hand, to collect the number of pregnancies provided in the present study; data collection would take at least 10 years and interfere with the contemporaneous applicability. A second limitation is the possibility of underreporting. Because data-retrieval was retrospective, only documented complications (by medically educated personnel) were included. Third, we need to take into account that for the present study, a survivor cohort was selected,

therefore not allowing the investigation of maternal mortality. Moreover, patients thought to be at high risk based on earlier studies, e.g. Eisenmenger syndrome and many Fontan patients, are generally advised against pregnancy or mainly patients at relatively good health achieve pregnancy. The risk of pregnancy in women with these complex heart diseases can therefore be underestimated in this study; nevertheless, it represents today's policies regarding pregnancy. Another limitation concerns the impossibility in this retrospective study to accurately quantify the severity of systemic and pulmonary ventricular volumes and function. Also the exclusion of miscarriage and abortion pregnancies may result in an underestimation of certain risks. For example, the reason for elective abortion in one patient was a clinically significant supraventricular arrhythmia with secondary heart failure. To include these pregnancies in the analyses would, however, lead to an underestimation of other complications that incorporated a certain gestational age to develop, i.e. hypertensive disorders. Moreover, the limitations associated with the low-risk contrast, the still relatively small cohort, and the lower incidence of complications and subsequent impossible internal validation need to be taken into account. The present cohort is representative for a CHD population receiving tertiary medical care, including patients with complex heart disease; caution, however, is needed when extrapolating the results to populations with another CHD distribution. In summary, the results should be interpreted with caution.

## Funding

This work was supported by Netherlands Heart Foundation Grant 2002 B125 to P.G.P. and the Interuniversity Cardiology Institute the Netherlands (ICIN). D.J.V. and A.A.V. are established investigators of the Netherlands Heart Foundation (grants D97.017 and 2006T037, respectively).

**Conflict of interest**: none declared.

## References

1. Drenthen W, Pieper PG, Roos-Hesselink JW, van Lottum WA, Voors AA, Mulder BJ, van Dijk AP, Vliegen HW, Yap SC, Moons P, Ebels T, Van Veldhuisen DJ. Outcome of pregnancy in women with congenital heart disease: a literature review. *J Am Coll Cardiol* 2007;**49**:2303–2311.
2. Siu SC, Sermer M, Colman JM, Alvarex 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. Prospective multicenter study of pregnancy outcomes in women with heart disease. *Circulation* 2001; **104**:515–521.
3. Siu SC, Colman JM, Sorensen S, Smallhorn JF, Farine D, Amankwah KS, Spears JC, Sermer M. Adverse neonatal and cardiac outcomes are more common in pregnant women with cardiac disease. *Circulation* 2002;**105**:2179–2184.
4. Khairy P, Ouyang DW, Fernandes SM, Lee-Parritz A, Economy KE, Landzberg MJ. Pregnancy outcomes in women with congenital heart disease. *Circulation* 2006; **113**:517–524.
5. Drenthen W, Pieper PG, Ploeg M, Voors AA, Roos-Hesselink JW, Mulder BJ, Vliegen HW, Sollie KM, Ebels T, van Veldhuisen DJ. Risk of complications during pregnancy after Senning or Mustard (atrial) repair of complete transposition of the great arteries. *Eur Heart J* 2005;**26**:2588–2595.
6. Drenthen W, Pieper PG, van der Tuuk K, Roos-Hesselink JW, Voors AA, Mostert B, Mulder BJ, Moons P, Ebels T, van Veldhuisen DJ. Cardiac complications relating to pregnancy and recurrence of disease in the offspring of women with atrioventricular septal defects. *Eur Heart J* 2005;**26**:2581–2587.
7. Drenthen W, Pieper PG, Roos-Hesselink JW, van Lottum WA, Voors AA, Mulder BJ, van Dijk AP, Vliegen HW, Sollie KM, Ebels T, van Veldhuisen DJ. Pregnancy and delivery in women after Fontan palliation. *Heart* 2006;**92**:1290–1294.
8. Drenthen W, Pieper PG, van der Tuuk K, Roos-Hesselink JW, Hoendermis ES, Voors AA, Mulder BJ, van Dijk AP, Yap SC, Vliegen HW, Moons P, Ebels T, van Veldhuisen DJ. Fertility, pregnancy and delivery in women after biventricular repair for double outlet right ventricle. *Cardiology* 2008;**109**:105–109.
9. Drenthen W, Pieper PG, Zoon N, Roos-Hesselink JW, Voors AA, Mulder BJ, van Dijk AP, Sollie KM, Vliegen HW, Ebels T, van Veldhuisen DJ. Pregnancy after biventricular repair for pulmonary atresia with ventricular septal defect. *Am J Cardiol* 2006;**98**:262–266.
10. Drenthen W, Pieper PG, Roos-Hesselink JW, Schmidt AC, Mulder BJ, Van Dijk AP, Vliegen HW, Sollie KM, Voors AA, Ebels T, van Veldhuisen DJ. Noncardiac complications during pregnancy in women with isolated congenital pulmonary valvar stenosis. *Heart* 2006;**92**:1838–1843.
11. Meijer JM, Pieper PG, Drenthen W, Voors AA, Roos-Hesselink JW, Van Dijk AP, Mulder BJ, Ebels T, van Veldhuisen DJ. Pregnancy, fertility, and recurrence risk in corrected tetralogy of Fallot. *Heart* 2005;**91**:801–805.
12. Vriend JW, Drenthen W, Pieper PG, Roos-Hesselink JW, Zwinderman AH, van Veldhuisen DJ, Mulder BJ. Outcome of pregnancy in patients after repair of aortic coarctation. *Eur Heart J* 2005;**26**:2173–2178.
13. Yap SC, Drenthen W, Pieper PG, Moons P, Mulder BJ, Klieverik LM, Vliegen HW, van Dijk AP, Meijboom FJ, Roos-Hesselink JW. Outcome of pregnancy in women after pulmonary autograft valve replacement for congenital aortic valve disease. *J Heart Valve Dis* 2007;**16**:398–403.
14. Yap SC, Drenthen W, Pieper PG, Moons P, Mulder BJ, Mostert B, Vliegen HW, van Dijk AP, Meijboom FJ, Steegers EA, Roos-Hesselink JW. Risk of complications during pregnancy in women with congenital aortic stenosis. *Int J Cardiol* 2008;**23**: 240–246.
15. Elkayam U, Bitar F. Valvular heart disease and pregnancy: part II: prosthetic valves. *J Am Coll Cardiol* 2005;**46**:403–410.
16. Sadler L, McCowan L, White H, Stewart A, Bracken M, North R. Pregnancy outcomes and cardiac complications in women with mechanical, bioprosthetic and homograft valves. *BJOG* 2000;**107**:245–253.
17. Sbarouni E, Oakley CM. Outcome of pregnancy in women with valve prostheses. *Br Heart J* 1994;**71**:196–201.
18. Vahanian A, Baumgartner H, Bax J, Butchart E, Dion R, Filippatos G, Flachskampf F, Hall R, Iung B, Kasprzak J, Nataf P, Tornos P, Torracca L, Wenink A, Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology. Guidelines on the management of valvular heart disease: The Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology. *Eur Heart J* 2007;**28**:230–268.
19. Warnes CA, Liberthson R, Danielson GK. Task force 1: the changing profile of congenital heart disease in adult life. *J Am Coll Cardiol* 2001;**37**:1170–1175.
20. Easterling TR, Chadwick HS, Otto CM, Benedetti TJ. Aortic stenosis in pregnancy. *Obstet Gynecol* 1988;**72**:113–118.
21. Lao TT, Sermer M, MaGee L, Farine D, Colman JM. Congenital aortic stenosis and pregnancy–a reappraisal. *Am J Obstet Gynecol* 1993;**169**:540–545.
22. Silversides CK, Harris L, Haberer K, Sermer M, Colman JM, Siu SC. Recurrence rates of arrhythmias during pregnancy in women with previous tachyarrhythmia and impact on fetal and neonatal outcomes. *Am J Cardiol* 2006;**97**:1206–1212.
23. Presbitero P, Somerville J, Stone S, Aruta E, Spiegelhalter D, Rabajoli F. Pregnancy in cyanotic congenital heart disease. Outcome of mother and fetus. *Circulation* 1994;**89**:2673–2676.
24. Spellacy WN, Handler A, Ferre CD. A case-control study of 1253 twin pregnancies from a 1982–1987 perinatal data base. *Obstet Gynecol* 1990;**75**:168–171.
25. Roberts WE, Morrison JC, Hamer C, Wiser WL. The incidence of preterm labor and specific risk factors. *Obstet Gynecol* 1990;**76**:85S–89S.
26. Smoking and pregnancy. www.uptodate.com.
27. Curtis SL, Marsden-Williams J, Sullivan C, Sellers SM, Trinder J, Scrutton M, Stuart AG. Current trends in the management of heart disease in pregnancy. *Int J Cardiol* 2009;**133**:62–69.
28. Ford AA, Wylie BJ, Waksmonski CA, Simpson LL. Maternal congenital cardiac disease: outcomes of pregnancy in a single tertiary care center. *Obstet Gynecol* 2008;**112**:828–833.
29. Siu SC, Sermer M, Harrison DA, Grigoriadis E, Liu G, Sorensen S, Smallhorn JF, Farine D, Amankwah KS, Spears JC, Colman JM. Risk and predictors for pregnancy-related complications in women with heart disease. *Circulation* 1997; **96**:2789–2794.
30. Thorne S, MacGregor A, Nelson-Piercy C. Risk of contraception and pregnancy in heart disease. *Heart* 2006;**92**:1520–1525.