Risk Assessment of the Cardiac Pregnant Patient

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Abstract

Women with heart disease are at increased risk for maternal and fetal complications in pregnancy. Therefore, all women with heart disease should undergo evaluation and counseling, ideally prior to conception, or as early in pregnancy as possible. In this article we will review the role of risk assessment, the history of development of the cardiac risk prediction tools, and the role of current cardiac risk prediction tools.

Key Words: Cardiac Risk Prediction, Pregnancy, Women with Heart Disease

Introduction

It has been estimated that 1-4% of pregnant women have some form of pre-existing cardiac disease.[1] Congenital heart disease (CHD) comprising the majority all cardiac lesions among pregnant women in high-income countries, while in middle- and low-income countries, rheumatic heart disease comprises at least one half of cardiac lesions encountered during pregnancy.[1] With rising maternal age and increasing prevalence of hypertension, diabetes, and obesity, the number of pregnant women with ischemic or hypertensive heart disease is expected to continue to rise. Pregnancy, which is associated with profound cardiovascular changes and higher risk of thrombosis, increases the risk of cardiovascular complications in women with pre-existing heart disease. In this article, we will review the role of risk assessment, the history of development of the cardiac risk prediction tools, and the role of current cardiac risk prediction tools.

Risk Assessment and Counselling

While women with heart disease are at increased risk for maternal and fetal complications in pregnancy, many of these women report they are unaware of pregnancy related risks and underestimate the severity of their heart disease.[2, 3] The unintended pregnancy rate among women with congenital heart disease in the United States is reported to be around 50%.[3-5] In the general obstetric population, preconception counseling can modify behavior, decrease adverse outcomes in pregnancy, and lead to fewer unintended pregnancies.[6] While the efficacy of preconception counseling on outcomes in pregnant women with heart disease has not been quantified, preconception counseling is universally recommended for all women with heart disease.

The most efficacious content, timing, and format of preconception counselling for heart disease has not been well studied. A recent study reported that a multi-disciplinary approach to preconception care for women with heart disease was well received by patients.[4] Ideally all women

with heart disease should undergo cardiac evaluation and counseling prior to conception. In those women who did not undergo preconceptual evaluation, baseline cardiac evaluation and risk counseling should be completed as early in pregnancy as possible. Preconception counseling should include obstetricians, cardiologists, obstetric anesthesiologists, and maternal fetal medicine physicians. It should assess and review the risks of pregnancy on the mother and the fetus, potential interventions to reduce maternal or fetal risk prior to pregnancy, the anticipated management course during pregnancy, and methods for pregnancy prevention.

While women with heart disease are recognized to be at an increased risk of maternal cardiac complications (cardiac arrhythmia and heart failure are the most common), they are also are at a higher risk of obstetrical complications (including postpartum hemorrhage, and gestational hypertension), and fetal complications (including miscarriage, preterm delivery, and intrauterine growth restriction). Potential for transmission of congenital heart disease to offspring and medication exposure risks to the fetus are additional considerations. Also there is data suggesting that pregnancy accelerates cardiac lesion progression.[7, 8] It is important to make women aware of this possibility given the potential implications on long term cardiac function and maternal life span.

Maternal risk evaluation can be accomplished by a detailed history, physical examination, percutaneous oximetry, 12 lead EKG and a transthoracic echocardiogram performed/interpreted by individuals with experience in evaluating congenital and acquired heart disease. Data obtained during clinical assessment should include New York Heart Association functional class, details of prior cardiac events (such as heart failure, stroke, or arrhythmias) or cardiac interventions. The above baseline assessment data can then be integrated into cardiac risk assessment tools that will be discussed in greater details below. While pregnancy in women at the highest cardiac risk is

generally not advisable, the associated risk estimates can provide clarity in expectations and management planning in those women who become pregnant.

As common medications used for treatment of cardiac disease are teratogenic during early embryogenesis,[7] a detailed discussion of medication risks and development of a plan regarding continuation or discontinuation over the pre and peri conception periods is valuable. Offspring of women with congenital heart disease have a 5-10% risk of having congenital heart disease, which is five times the general population risk. The risk can be as high as 50% if the maternal cardiac pathology has an autosomal dominant inheritance pattern.[7] Therefore, a formal genetics evaluation should be offered for all women with congenital heart disease to evaluate the risk of recurrence and discuss potential options for risk reduction.

Management during the pregnancy is multidisciplinary, with maternal fetal medicine and cardiology. The frequency of visits, and need for additional subspecialists is dependent on the underlying cardiac lesion. Repeat cardiac assessment should occur with onset of any new cardiac symptoms, and in the third trimester. Typically, a vaginal delivery is appropriate, however there are select cases where a cesarean section is preferred. The peripartum and immediate postpartum periods have significant fluid shifts and are associated with increased risk of adverse outcomes. It is important to ensure a patient with moderate to severe risk for adverse cardiac events is delivering at a hospital capable of handling any complications that may occur during delivery or postpartum.

For women who do not desire pregnancy for either personal or health reasons, a discussion of safe and effective contraception options is imperative. Many women with heart disease have not discussed contraception with their providers, or have received incorrect information regarding safe and effective contraceptive options.[3, 5] Pregnancy prevention is the ideal way to prevent

unnecessary maternal and fetal risks related to pregnancy. Emergency contraception is also safe for women with heart disease and early pregnancy termination is an optimal option for women if pregnancy is not desired or if the morbidity and mortality related to pregnancy is deemed too high.

Development of Cardiac Risk Assessment Tools

Until the development of cardiac risk assessment tools, risk prediction was based on personal experience, case series, or case reports. Large case series reported the deleterious effects of poor maternal New York functional class or maternal cyanosis in pregnant women with congenital heart disease,[9, 10] while high maternal and fetal mortality was reported in pregnant women with Eisenmenger syndrome. These early studies not only identified predictors of maternal cardiac complications that are currently utilized, they also highlighted potential problems with observational studies such as retrospective review, referral bias, ascertainment bias, and adjustment for confounding in data analysis. Currently, Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement is useful in evaluating whether key features of the study design are in place to mitigate bias in observational studies, including: 1) Ensuring the study population is **representative** of the target population; 2) **Consecutive** enrollment, 3) **Prospective** data collections; 4) **Standardized definitions for data** (baseline and outcomes) and quality control measures.[11]

The Canadian Cardiac Disease in Pregnancy (CARPREG) study was a national multi-center study that prospectively enrolled pregnant women with preexisting congenital, acquired, or arrhythmic heart disease and follow them during pregnancy and until the 6th postpartum month (Table 1). The CARPREG study was conducted using infrastructure and quality controls identical to that used for multi-center clinical trials (steering committee, operational manual, informed consent, standardized data definitions, prespecified primary and secondary endpoints, and

independent adjudication of events).[12] The CARPREG risk score was derived and validated from the above study data, therefore fulfilling the Strobe criteria and ensuring representativeness within the diverse population in Canadian cities.

The 2001 CARPREG study identified 4 baseline maternal characteristics which were independent predictors of a primary maternal cardiac event, which was a composite outcome comprising of cardiac death, stroke, heart failure, or sustained arrhythmia requiring treatment. (Tables 1 and 2) Aortic dissection and systemic thromboembolism were considered as cardiac events but none occurred during the study. The CARPREG risk score (or predictive index) combined individual predictors to classify that individual into one of several classes of risk for a cardiac event. As the odds ratio of the 4 predictors were similar and to simplified calculations, the 4 predictors were assigned equal weights, and the overall risk score was a sum of points. Risk scores of 0, 1, or >1 correspond to maternal cardiovascular event rates during pregnancy of 5%, 27%, or 75%, respectively. Additionally, the CARPREG risk score was also predictive of deterioration in maternal functional class and need for urgent cardiac intervention in pregnancy or postpartum period. While the CARPREG score was validated by other groups, with some reporting that adding other predictors enhances the prediction accuracy,[13] important limitations was the modest sample size and the small number of patients with very high risk cardiac lesions (such as pulmonary hypertension).

Investigators from Belgium and Netherlands, the Zwangerschap bij Aangeboren HARtAfwijking [Pregnancy in Women with Congenital Heart Disease] group - ZAHARA-I) performed a retrospective study of pregnant women with CHD and derived a weighted risk score (ZAHARA-I).[14] (Tables 1 and 2) ZAHARA-I assigned points ranging from 0.75 to 4.25 to eight

predictors, and the overall risk score was a sum of points ranging from 0 to >3.51 correspond to maternal cardiovascular event rates ranging from of 2.9% to 70.0%, respectively.[14] While some of the ZAHARA-I predictors overlap with those identified by CARPREG, additional predictors were identified, perhaps related to differences in patient population, larger sample size, and expanded endpoint definitions. While ZAHARA I had an expanded list of predictors, it required a calculator to generate the risk estimates, and its applicability to pregnant women without CHD has not been established.

Both of the abovementioned risk scores used multivariable logistic regression analysis to mathematically define the relationship between some baseline variables and binary outcome(s) of interest.[15] Thus it is important to be aware of some of the following caveats of multivariable logistic regression analysis: 1) Reproducibility of the predictors identified by the analysis increases with the sample size;[16] 2) The number of outcomes should be at least 10 times the number of risk factors being considered;[15] 3) Failure to account for candidate risk factors that are closely correlated (collinear) can lead to spurious results that cannot be duplicated in other population; [15] 4) all pregnancies need to have complete data for every risk factor that is being considered. A checklist to assess the quality of a risk score has been proposed.[17]

Risk stratification can also be performed by incorporating lesions specific risks. The current lesion-specific risk assessment tool is the modified World Health Organization (mWHO) classification (Table 3). The mWHO was first introduced in 2011 as a qualitative classification based on expert consensus without numerical values assigned to the various risk categories, and thus is not considered a risk score.[18, 19] This classification tool incorporates information predominantly based on the type of cardiac lesion with some information on lesion severity, and

categorizes women with cardiac disease into five classes of increasing cardiovascular risk (mWHO classes I, II, II-III, III and IV). Although simple to apply clinically, it is important to understand that the mWHO classification was primarily based on lesion specific risks, with limited or no consideration of other risk factors such as prior cardiac events, functional status, and ventricular function, [12, 14, 20] which increases risk of cardiac events in pregnancy. For example, the CARPREG risk factors can further risk stratify pregnancies within each WHO classes (Figure 1).[21] Secondly, the mWHO classification is difficult to apply when the maternal cardiac diagnosis is not included in the list of lesions. A recent study reported an overall 12.5 % cardiac event rate in those pregnancies that cannot be assigned to one of the original mWHO classes.[21] Most importantly, the mWHO classification is not based on original patient level data, but a result of expert consensus using level "C" evidence (consensus opinion of experts and/or small studies, retrospective studies or registries).

The performance of a risk stratification tool is typically expressed as discrimination (accuracy in predict who will or will not experience a complication) and calibration accuracy (agreement between predicted and actual frequency of complications across different risk groups). Discrimination usually measured by the c statistic or Area under the Receiver Operating Characteristic (AUROC) curve], with 0.50 being no better than random chance, 0.60 to 0.69 being poor, 0.70 to 0.79 being fair, 0.80 to 0.89 being good, and $\geq$0.90 being excellent.[22] Calibration is expressed by Hosmer-Lemishow Chi square goodness of fit statistic, with $p<0.05$ indicating a significant overall difference between observed and expected frequency of events across the risk groups. Several studies comparing the performance of CARPREG risk score, ZAHARA-I risk score, and mWHO classification system, reported that mWHO has better discrimination than CARPREG or ZAHARA.[19, 23-26] However, even when studies reported that mWHO was the best

at predicting cardiovascular risk, the discriminative accuracy of the mWHO score was at most 'fair' (AUROC 0.71 to 0.77). A consistent finding is that CARPREG, Zahara I, and mWHO do not have both good discrimination and calibrative accuracy when assessed in other populations. Important reasons for this include the wide variations with regard to the cardiac lesions included, the definition for predictors and outcomes, the nature and severity of cardiac lesions between regions, differences in management and follow-up between centres. While external validation will provide a real world measure of performance, the definition of predictors and outcomes in this type of external validation study must be identical to the original study. Another caveat is that validation set needs to have an adequate number of outcomes – it has been suggested that the validation study has to have at least 100 patients with the outcome of interest and 100 patients without the outcome of interest, to be able to definitively assess the discrimination and calibration of the prediction rule.[27]

Current Cardiac Risk Classification Tools

Carpreg II study was a continuation of the CARPREG study at the Toronto lead site together with another high volume obstetric centre, utilizing the same study infrastructure and protocol as the original CARPREG national study. The CARPREG II study reported on consecutive prospectively recruited pregnant women with heart disease from 1994 to 2014, who were cared by same team of physicians and in later years, within the context of maternal cardiac clinics (Tables 1). As the study sample was almost 4 times that of the original CARPREG study, additional outcome events were identified although heart failure and cardiac arrhythmia remained the most common maternal cardiac complications. Carpreg II risk score incorporated the original CARPREG predictors and added lesion specific and process of care predictors. Unlike the original CARPREG risk scores, the 10 independent predictors of cardiac events were associated with

different levels of risk and thus were assigned different weights (points). Three predictors (poor maternal functional class or cyanosis, prior cardiac events or arrhythmias, mechanical valve) had the highest level of risk and thus were assigned 3 points each. The CARPREG II risk score was the sum of the points corresponding to the presence or absence of each of the 10 predictors (Table 2). Range of points of 0 to > 4 points corresponded to cardiac event rates ranging from 5% to 41% (Table 2: Figure 2).[21]

CARPREG II risk score also is applicable when secondary outcome events (urgent cardiac procedures during pregnancy and within 6 weeks postpartum or deterioration of $\geq$ 2 functional class during the antepartum period). Carpreg II risk score was validated in the CARPREG study using split sample technique. When compared with CARPREG, ZAHARA-I, and mWHO, the CARPREG-II risk score not only had the highest discriminative accuracy (c statistic) in the validation set, but was the only risk classification tool that had good calibrative accuracy (no significant difference between expected and observed risk across the risk groups)(Figure 3).[21] While the CARPREG II risk score has the potential to provide the most comprehensive assessment of maternal cardiovascular risks as it incorporated general risk factors, lesion-specific risk factors, and process of care factors (Figure 2),[21] it has not been independently validated in other patient populations.

Its most recent version published as part of the 2018 European Society of Cardiology (ESC) Guidelines, the original mWHO classification was updated to include 12 additional lesion categories (Table 3). In addition, each risk class was assigned a numerical value corresponding to maternal cardiac risk estimate ranging from 2.5% to 100%, but the basis of these risk estimates was not stated.[1] Highest-risk cardiac lesions (mWHO class IV) are considered to be associated with significant maternal mortality and women with these conditions should either be counseled

against pregnancy, or managed in centres where maximum surveillance is possible from a cardiac and obstetric standpoint. There has been no validation of the updated mWHO classification

Cardiac Risk Classification Tools Clinical Practice, Caveats, Gaps and Opportunities

All of the existing risks stratification tools should be seen as a starting point to guide clinicians while counseling women with heart disease.[28] Clinicians should familiarize themselves with the scope and limitations of each scoring system and choose the method of risk assessment which is the most feasible for their practice setting. If they opt to use one of the risk scores, they should consider incorporating lesion-specific risks for those patients with high risk lesions before making clinical recommendations (Figure 1). One approach is to identify pregnancies in women with cardiac lesions at particularly risk for cardiac mortality, but may not be under represented in studies from which risk scores were developed. Infrequent encountered high cardiac risk lesions include mechanical valves, cardiomyopathy from any cause with severe left ventricular systolic function, previous peripartum cardiomyopathy with residual left ventricular systolic dysfunction, severe symptomatic mitral or aortic stenosis, Eisenmenger syndrome, Fontan with systemic ventricular dysfunction, Marfan or hereditary thoracic aortic syndrome with aortic dilatation, vascular Ehlers-Danlos syndrome, or spontaneous coronary artery dissection. For pregnancies in women without the abovementioned high-risk lesions, CARPREG II risk score could be used, with subsequent modification after integrating patient specific considerations (include exercise testing, cardiac imaging data, compliance, co-morbid conditions, and socio-economic status). Conversely, if clinicians choose to use the mWHO risk-classification system, this should not be used in isolation without considering predictors such as prior history of heart failure and arrhythmias which further augments maternal cardiovascular risk (Figure 1). Importantly, cardiac risk assessment should

always incorporate clinical judgment in addition to the use of risk scores or risk classification systems.

While interpreting risk, it is important to remember that the cardiac event rate in the lowest risk group can be as high as 5%, thus "low" risk is the not the same as "no" risk.[1, 12, 14, 21]

Clinicians must also remember that current risk scores and risk classification methods focused only on maternal cardiac risk, but 'pregnancy risk' also include the obstetric and fetoneonatal complications, as well as long term risk of cardiac complications or lesion progression,[8] which are arguably more frequent and equally, if not more life-transforming. The multidisciplinary team should therefore ensure that the risk assessment provided covers all these aspects of health, which are important in shared decision-making regarding continuation versus termination of pregnancy, obstetric surveillance, decisions regarding the mode of delivery and resource allocation.

Future tools for risk prediction in pregnant women with heart disease will need to evolve and have the predictive capability to estimate the risk both maternal and fetoneonatal complications, provide risk estimates that are specific to an individual patient's lesion, while considering socioeconomic status, patient specific factors (lifestyles, health care behavior, compliance), access to specialty care, and the nature of health system.

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Figure Legends

Figure 1: The overall frequency of pregnancy related cardiac complications in each modified World Health Organization (mWHO) class is shown in red. The risk of complications within each mWHO classes is further stratified according to CARPREG risk scores of 0 (Carpreg 0), 1 (Carpreg 1), and >1 (Carpreg>1). [Modified from reference [21]]

Figure 2: The CARPREG II risk score is based on 10 predictors, each assigned a weighted point. The sum of points represents the risk score. Risk scores are categorized into the 5 groups shown on the x axis. The predicted (blue) and observed frequency of cardiac events in the derivation (purple) and validation (red) groups are shown on the y axis. [Modified from reference [21]]

Figure 3: Comparative graph showing the predicted (in yellow) and observed (in blue) rate of cardiovascular complications as a function of risk group as calculated by CARPREG II risk Score, modified World Health classification system with risk estimates for high income countries (mWHO), CARPREG risk score, and the ZAHARA I risk score. C denotes c statistic or discriminative accuracy. HL-X^2 denotes Hosmer-Lemeshow Chi Square goodness of fit statistic, a measure of calibrative accuracy.[Modified from reference [21]]

Table 1: Summary of Cardiac Risk Classification Tools [Single center studies and smaller studies reporting predictive role of cardiopulmonary testing, N-terminal pro-brain natriuretic peptide, sub-pulmonary ventricular systolic dysfunction were not included]

		RISK SCORES			CLASSIFICATION SYSTEM
	Study and Year of Publication	**CARPREG II [21] 2018**	**ZAHARA 1 [14] 2010**	**CARPREG [12] 2001**	**mWHO [1, 18] 2011 and 2018***
	Data Source	Multi-centre, Canada	Multi-centre, Europe	Multi-centre, Canada	Expert opinion
	Study Design	Consecutive, prospective	Retrospective	Consecutive, prospective	
	Cardiac lesions included	64% CHD, 23% acquired, 13% arrhythmias	100% CHD	74% CHD, 22% acquired, 4% arrhythmias	CHD, acquired, and arrhythmias
	Gestational age at entry into study	< 20 weeks' gestation in 65% of pregnancies	Not stated	< 20 weeks' gestation in 69% of pregnancies	-
	Latest follow up	6 months after delivery	6 months after delivery	6 months after delivery	-
	Independent verification of events	Yes	No	Yes	-
Primary cardiac events	**Death**	Cardiac Death	-	Cardiac death	- [a]
	Heart Failure	• Pulmonary edema • Right heart failure	Heart failure requiring treatment	Pulmonary oedema	_ a
	Arrhythmias	Sustained symptomatic arrhythmia requiring treatment	Arrhythmias requiring treatment	Sustained symptomatic arrhythmia requiring treatment	- [a]
	Other cardiovascular outcomes	• Stroke or transient ischemic attack • Cardiac arrest • Myocardial infarction • Vascular dissection • Cardiac thromboembolism	• Stroke • Myocardial infarction • Endocarditis • Thromboembolism	• Stroke • Cardiac arrest	- [a]
Secondary cardiac events		• Antepartum decline ≥ 2 NYHA • Urgent cardiac procedure up to the 6th postpartum week	-	• Antepartum decline ≥ 2 NYHA • Urgent cardiac procedure up to 6th postpartum month	- [a]

CHD, congenital heart disease; NYHA, New York Heart Association functional class; mWHO, Modified World Health organization; [a] Not specifically mentioned other than maternal cardiac eventual rate

Table 2: Summary of How Pregnancy Risk Scores and Risk Estimates Are Calculated

	RISK SCORES		
	CARPREG II [21] (Points in Brackets)	**ZAHARA 1 [14] (Points in Brackets)**	**CARPREG [12]**
Functional Predictors	• Cardiac event (heart failure, transient ischemic attack, stroke, or arrhythmia requiring treatment) prior to current pregnancy[a] (3) • Baseline NYHA III/IV or Cyanosis (3) • Systemic ventricular ejection fraction <55% (2) • Left heart obstruction (mitral valve area<2 cm^2 or aortic valve area<1.5 cm^2, or peak left ventricular outflow tract gradient>30 mmHg) or at least moderate-severe mitral regurgitation (2)	• History of arrhythmias (1.5) • Cardiac medications before pregnancy (1.5) • NYHA ≥ II prior to pregnancy (0.75) • Left heart obstruction (2.5) • Moderate/ Severe systemic atrioventricular valve regurgitation (0.75) • Moderate/ Severe pulmonary atrioventricular valve regurgitation (0.75 points)	**1 point each for** • Cardiac event (heart failure, transient ischemic attack, stroke, or arrhythmia requiring treatment) prior to current pregnancy[a] • Baseline NYHA III or IV or cyanosis • Systemic ventricular ejection fraction <40% • Left heart obstruction (mitral valve area<2 cm^2 or aortic valve area<1.5 cm^2, or peak left ventricular outflow tract gradient>30 mmHg)
Lesion Specific Predictors	• Mechanical valve (3) • Pulmonary hypertension [b] (2) • Coronary artery disease [c] (2) • High-risk aortopathy [d] (2)	• Mechanical valve (4.25) • Corrected or Uncorrected cyanotic heart disease (1.0)	
Process Predictor	• No prior cardiac interventions [e] (1) • Late pregnancy assessment [f] (1)		
Sum of Points and Corresponding Cardiac Risk	• 0 to 1 point = 5% • 2 points = 10% • 3 points = 15% • 4 points = 22% • > 4 points = 41%	• 0–0.50 point = 2.9%, • 0.51–1.5 points = 7.5 • 1.51–2.50 points = 17.5% • 2.51–3.50 points = 43.1% • >3.51 = 70.0%	• 0 point = 5%, • 1 point = 27% • > 1 points = 75%

[a] excluding events preceding prior cardiac surgery; [b] right ventricular systolic pressure ≥ 50 mmHg in the absence of right ventricular outflow tract obstruction; [c] angiographically proven coronary artery obstruction or past myocardial infarction; [d] Marfan syndrome, bicuspid aortopathy with aortic dimension >45 mm, Loeys-Dietz syndrome, vascular Ehlers-Danlos syndrome, or prior aortic dissection or pseudoaneurysm); [e] no prior repair of congenital lesion, valve repair/replacement, or percutaneous/surgical treatment of arrhythmia; [f] first antenatal assessment > 20 weeks gestation; NYHA, New York Heart Association functional class

Table 3. Modified World Health Organization Classification of Cardiovascular Risk (Additional lesions or clarifications added in 2018 Guidelines Are Bolded and in Italics) [1, 18]

mWHO Class	Cardiac lesions	Maternal Cardiac Risk Assigned by 2018 Guidelines Authors [a]	Clinical Application
Class I	• Small or mild pulmonary stenosis, patent ductus arteriosus, mitral valve prolapse • Successfully repaired simple lesions (atrial or ventricular septal defect, patent ductus arteriosus, anomalous pulmonary venous connection) • Atrial or ventricular ectopic beats, isolated	2.5 to 5%	No detectable increased risk of maternal mortality and no/mild increase in morbidity
Class II	• Unoperated atrial or ventricular septal defect • Repaired tetralogy of Fallot • Most arrhythmias (***supraventricular arrhythmias***) • ***Turner syndrome without aortic dilation***	5.7 to 10.5%	Small increase in maternal risk mortality or moderate increase in morbidity
Class II or III (depending on individual)	• Mild left ventricular impairment (***EF>45%)*** • Hypertrophic cardiomyopathy • Native or tissue valvular heart disease not considered WHO I or IV • Marfan or other ***HTAD synd***rome without aortic dilatation • Aorta <45 mm in association with bicuspid aortic valve pathology • Repaired coarctation • ***Atrioventricular septal defect***	10 to 19%	Intermediate increased risk of maternal mortality or moderate to severe increase in morbidity
Class III	• ***Moderate left ventricular impairment (EF 30-45%)*** • Previous peripartum cardiomyopathy without residual left ventricular impairment • Mechanical valve • ***Systemic right ventricle with good or mildly decreased ventricular function*** • ***Fontan circulation if otherwise well and the cardiac condition uncomplicated*** • Unrepaired cyanotic heart disease	19 to 27%	Significantly increased risk of maternal mortality or severe morbidity. Expert counselling required. If pregnancy is decided upon, intensive specialist cardiac and obstetric monitoring needed throughout pregnancy, childbirth and the puerperium.

	• Other complex congenital heart disease • **Moderate mitral stenosis** • **Severe asymptomatic aortic stenosis** • Moderate aortic dilation (40–45 mm in Marfan syndrome or ***other HTAD***, 45–50 mm in bicuspid aortic valve, ***Turner syndrome ASI 20-25mm/m^2, tetralogy of Fallot <50mm***) • ***Ventricular tachycardia***		
Class IV	• Pulmonary arterial hypertension • Severe systemic ventricular dysfunction (EF<30% or NYHA class III-IV) • Previous peripartum cardiomyopathy with any residual left ventricular impairment • Severe mitral stenosis • Severe symptomatic aortic stenosis • ***Systemic right ventricle with moderate or severely decreased ventricular function*** • Severe aortic dilatation (>45 mm in Marfan syndrome or ***other HTAD***, >50 mm in bicuspid aortic valve, ***Turner syndrome ASI >25mm/m^2, tetralogy of Fallot >50mm***) • ***Vascular Ehlers-Danlos*** • Severe (re)coarctation • ***Fontan with any complication***	40 to 100%	Extremely high risk of maternal mortality or severe morbidity; pregnancy contraindicated. If pregnancy occurs termination should be discussed. If pregnancy continues, care as for class III

[a] Basis of risk estimates not provided ; ASI, aortic size index; EF, left ventricular ejection fraction; HTAD, heritable thoracic aortic disease; NYHA, New York Heart Association functional class; mWHO, modified World Health Organization

Figure 1

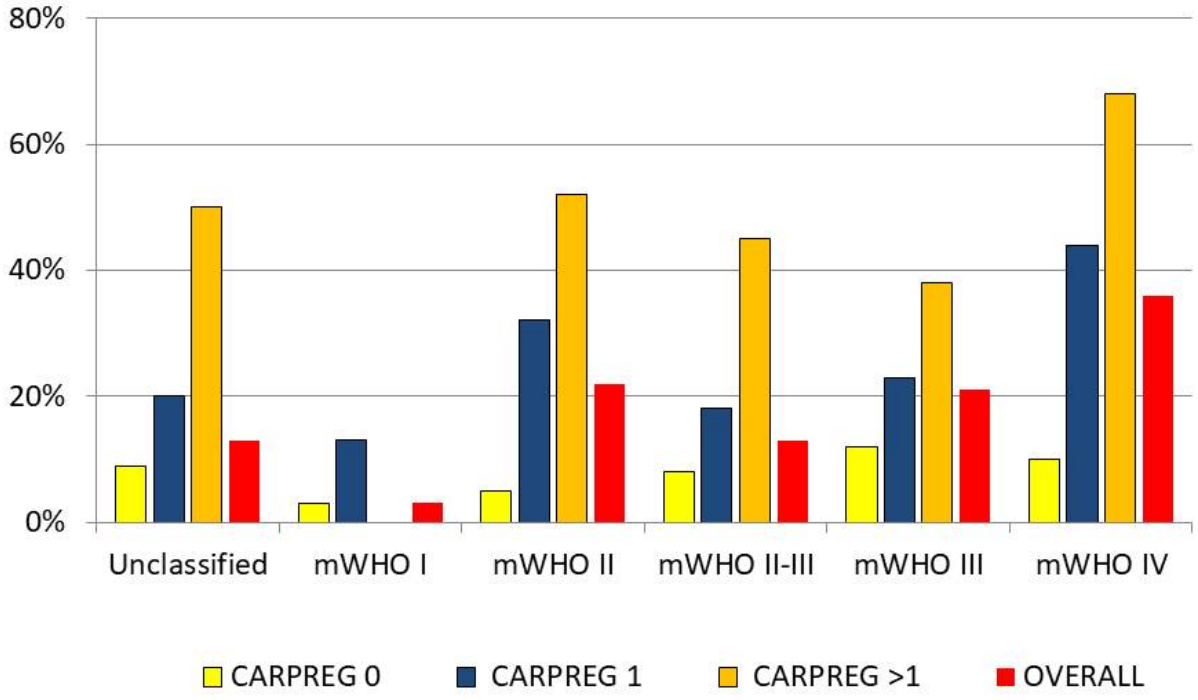
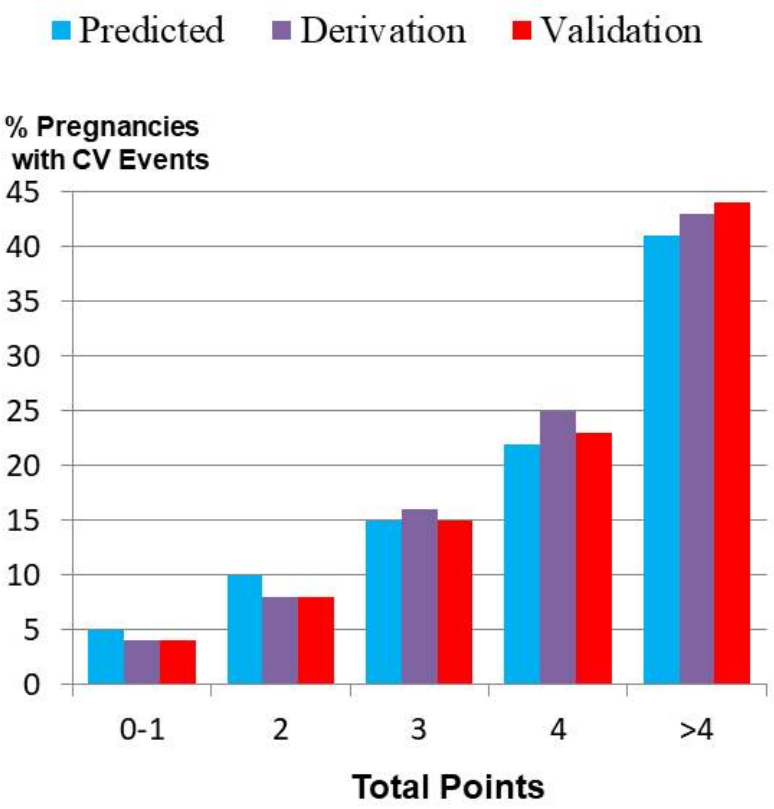
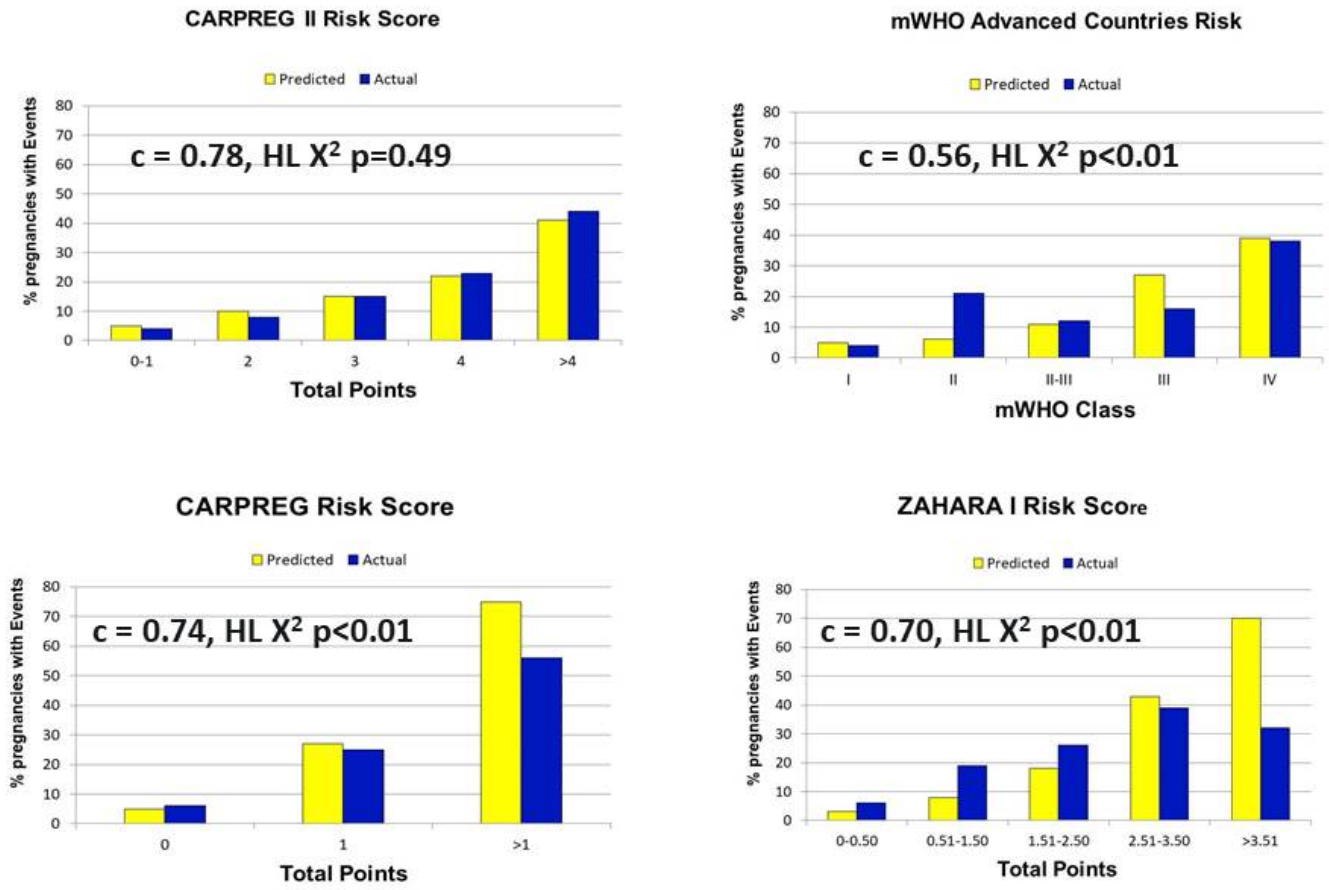

80%
60%
40%
20%
0%
Unclassified
mWHO I
mWHO II
mWHO II-III
mWHO III
mWHO IV
CARPREG 0
CARPREG 1
CARPREG >1
OVERALL

Figure 2



PREDICTOR	POINTS
History of cardiac events or arrhythmias	3
Baseline NYHA III-IV or cyanosis	3
Mechanical valve	3
Ventricular dysfunction	2
High risk left-sided valve disease/left ventricular outflow tract obstruction	2
Pulmonary hypertension	2
Coronary artery disease	2
High risk aortopathy	2
No prior cardiac intervention	1
Late pregnancy assessment	1

Figure 3


CARPREG II Risk Score
Predicted
Actual
% pregnancies with Events
c = 0.78, HL X² p=0.49
0-1
2
3
4
>4
Total Points
mWHO Advanced Countries Risk
Predicted
Actual
% pregnancies with Events
c = 0.56, HL X² p<0.01
I
II
II-III
III
IV
mWHO Class
CARPREG Risk Score
Predicted
Actual
% pregnancies with Events
c = 0.74, HL X² p<0.01
0
1
>1
Total Points
ZAHARA I Risk Score
Predicted
Actual
% pregnancies with Events
c = 0.70, HL X² p<0.01
0-0.50
0.51-1.50
1.51-2.50
2.51-3.50
>3.51
Total Points