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Charlene Bredy[1,†], Fanny Deville[1,†], Helena Huguet[2], Marie-Christine Picot[2], Gregoire De La Villeon[1], Hamouda Abassi[1], Martina Avesani [3], Laetitia Begue[4], Gilles Burlet[4], Pierre Boulot[4], Florent Fuchs[4] and Pascal Amedro [3,5,*]

1 Paediatric and Congenital Cardiology Department, M3C Regional Reference CHD Centre, University Hospital, 34295 Montpellier, France;

2 Epidemiology and Clinical Research Department, University Hospital, 34295 Montpellier, France;

3 Paediatric and Congenital Cardiology Department, M3C National Reference Centre, Bordeaux University Hospital, Avenue de Magellan, 33 604 Bordeaux, France;

4 Gynaecology and Obstetrics Department, University Hospital, 34295 Montpellier, France; and 5IHU Liryc, Electrophysiology and Heart Modelling Institute, Bordeaux University Foundation, Av. du Haut Lévêque, 33600 Pessac, France

Keywords

Congenital heart disease _ Pregnancy _ Risk score _ Maternal complication _ Cardiovascular

Clinical Trial Registration:

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† The first two authors contributed equally to the study.

* **Corresponding author.**

Tel: +33 (0) 5 24 54 92 19, Fax: +33 5 57 65 66 63, Email: pascal.amedro@chu-bordeaux.fr

Background

Management of pregnancy and risk stratification in women with congenital heart diseases (CHD) are challenging, especially due to physiological haemodynamic modifications that inevitably occur during pregnancy.

Aims

To compare the accuracy of the existing pregnancy cardiovascular risk scores in prediction of maternal complications during pregnancy in CHD patients.

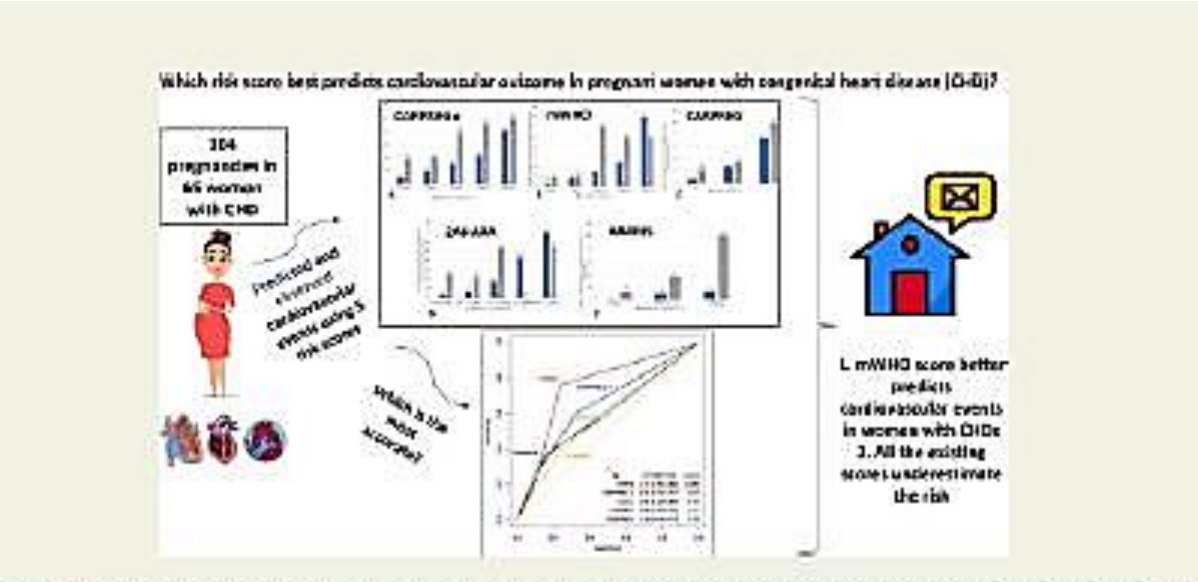
Methods and results

From 2007 to 2018, all pregnant women with a CHD who delivered birth after 20 weeks of gestation were identified. The discriminating power and the accuracy of the five existing pregnancy cardiovascular risk scores [CARPREG, CARPREG II, HARRIS, ZAHARA risk scores, and modified WHO (mWHO)] were evaluated. Out of 104 pregnancies in 65 CHD patients, 29% experienced cardiovascular complications during pregnancy or postpartum. For the five scores, the observed rate of cardiovascular events was higher than the expected risk. The values of area under the ROC curve were 0.75 (0.62–0.88) for mWHO, 0.65 (0.53–0.77) for CARPREG II, 0.60 (0.40–0.80) for HARRIS, 0.59 (0.47–0.72) for ZAHARA, and 0.58 (0.43–0.73) for CARPREG.

Conclusion

The modified WHO classification appeared to better predict cardiovascular outcome in pregnant women with CHD than the four other existing risk scores.

Graphical Abstract



Introduction

Since the end of the 20th century, advances in surgical and medical care have significantly improved the prognosis and quality of life of patients with congenital heart diseases (CHD).1 Currently, women with CHD expect to experience a 'normal' life and express a strong desire for pregnancy and maternity. Nevertheless, heart disease remains the first cause of non-obstetrical death during pregnancy2; therefore, it seems essential in women with CHD to assess maternal risk before conception and to individualize monitoring methods. However, given clinical, anatomical, and haemodynamic heterogeneity of these patients, management of pregnancy and risk stratification in this specific population remains challenging. Moreover, physiological and haemodynamic changes that inevitably occur during pregnancy, such as a significant increase in cardiac output and an increased thromboembolic risk due to hypercoagulability, may destabilize the underlying cardiac disease and increase the risk of maternal, foetal, and obstetrical complications.3,4

In the past decade, five scores have been used to predict cardiovascular maternal complications in women with cardiovascular heart diseases: HARRIS, ZAHARA, CARPREG I, the modified WHO (mWHO) classification,3,5–7 and, more recently, the CARPREG II classification, intending to improve maternal risk stratification.8 Therefore, in clinical practice, it is necessary to determine which classification stands as the most accurate in CHD, to reduce variability and allow better comparison and benchmark in this heterogeneous population. Indeed, except for the HARRIS score, these classifications have not been specifically designed for the CHD population and may omit specific conditions such as CHD-related pulmonary hypertension. Therefore, we aimed to compare the accuracy of the five existing cardiovascular pregnancy risk scores, including the recent CARPREG II score, in prediction of maternal complications during pregnancy in female patients with CHD.

Method

Study design and population

This retrospective study was carried out from January 2007 to June 2018 in a tertiary-care paediatric and adult congenital cardiology reference centre (Montpellier University Hospital, France). We identified in the database of our institution, all adult women with CHD who underwent at least one pregnancy during this period, leading to childbirth, spontaneous miscarriage, medical or voluntary termination of pregnancy. We excluded patients with early spontaneous miscarriage (before 26 weeks of gestation) and non-congenital cardiopathy.

Patients' characteristics

Demographic data, the type of CHD according to the ACC-CHD classification, and the complexity of CHD according to the Bethesda classification, were collected.9,10 The following clinical data were also obtained from medical records: age at the beginning of pregnancy, cardiological and obstetrical background, medications, type and number of prior cardiac procedures (cardiac surgery, prosthetic valve, electrophysiology procedures, or cardiac catheterization), heart failure according to the New York Heart Association (NYHA) functional class, arterial hypertension, pulmonary hypertension, cyanosis (oxygen saturation <90%), systolic function of the systemic ventricle, valvular insufficiency or stenosis,

ventricular dilatation, aortic dilatation, electrocardiogram data, Natriuretic B peptide, and haemoglobin (*Table 1*).

Cardiovascular pregnancy risk assessment

The expected maternal cardiovascular pregnancy risk was calculated using each one of the five existing scores, from baseline characteristics (e.g. CARPREG, ZAHARA, Harris, CARPREG II, and mWHO).3,7,8,11–14 For each patient, the five scores were performed by three investigators (two senior congenital cardiologists and one fellow) who reviewed the cardiovascular medical records. The investigators were blinded to each other's evaluations, as well as to the actual patient outcome during each pregnancy, delivery, and postpartum. A summary of the main differences between the different scales is shown in Supplementary material online, *Table S1*.

Cardiovascular events assessment

Cardiovascular outcomes were defined as the occurrence, during pregnancy, at the time of delivery, and up to 3 months post-partum, of any of the following events: cardiovascular death, heart failure (new-onset or NYHA functional class deterioration), antiarrhythmic drug initiation, thrombo-embolic complications (pulmonary embolism, vascular cerebral stroke), infectious endocarditis, resuscitated cardiac arrest, myocardial infarction, aortic dissection, occurrence or worsening of aortic dilatation, occurrence or worsening of ventricular dilatation, occurrence or worsening of a valvular insufficiency or stenosis, and deterioration of systolic function of the systemic ventricle.

Formal aspects

The study was conducted in compliance with the Good Clinical Practices protocol and Declaration of Helsinki principles. It was approved by the Montpellier University Hospital Institutional Review Board (2019_IRB-MTP_12–23) and registered on ClinicalTrials.gov (NCT04221048). Informed consent was obtained from all patients.

Statistical analysis

The study population was described with means and standard deviations (SDs) for quantitative variables and with frequencies for qualitative variables. The continuous variable distributions were tested using the Shapiro–Wilk test. Quantitative variables were compared using the Student's *t*-test when the distribution was Gaussian and with the Mann–Whitney test, otherwise. For qualitative variables, groups were compared using the $\chi 2$ test or Fisher's exact test. We compared the maternal risk predicted by these different scores to the appearance of cardiovascular events during pregnancy, childbirth, and a 3-month post-partum follow-up. The evaluation of the correlation of the results of the different scores for each pregnancy and of the maternal cardiovascular event is established by a ROC curve. ROC curves were drawn by plotting the sensitivity against (1–the specificity) for each pregnancy cardiovascular risk score. The area under the ROC curve (AUC) with its 95% confidence interval (95% CI) was calculated to evaluate the most discriminant score.

We performed a parallel double-blind assessment for each pregnancy, using each score by two senior physicians and one fellow. We compared the estimation of the risks established by 'senior' vs. 'junior' judges and their inter-observer reproducibility despite the difference in expertise. The agreement of pregnancy cardiovascular risk scores between junior and senior judges was assessed by the weighted Kappa coefficient with its 95% CI. The statistical significance was set at 0.05, and analyses were performed using the Statistical Analysis Systems Enterprise Guide version 4.3 (SAS Institute, Cary, NC, USA).

Results

Patient characteristics

Between January 2007 and June 2018, 70 patients with CHD were identified from our database and eligible for the study, with an overall number of 121 pregnancies. After excluding 15 pregnancies with spontaneous abortion before 26 weeks of gestation and 2 pregnancies with missing data on the cardiovascular outcome, a total of 65 patients were analysed, corresponding to 104 pregnancies, and resulting in 104 babies born at a mean of 38 ± 3 weeks of gestation (ranging from 24 to 42 weeks of gestation). We counted between 1 and 6 pregnancies per patient (mean 1.9 ± 1.0 pregnancies per patient and 1.5 ± 0.8 deliveries per patient), with 7 (7%) twin pregnancies. Most patients (*n* = 65; 63%) were nulliparous. The maternal age at delivery ranged from 18 to 41 years old (mean 29 ± 6 years). The gestational age at delivery ranged from 24 to 42 weeks (mean 39 weeks of gestation ± 3 days). Caesarean section surgery was performed in 31 (32%) cases, of which 13 were due to the CHD and one to a maternal cardiovascular event (*Table 1*).

In terms of disease severity, according to the Bethesda classification, 26% (*n* = 17) of the cohort had a simple CHD, 55% (n = 36) a moderate CHD, and 18% (*n* = 12) a complex CHD. Of all these patients, 62% (*n* = 64) underwent 1–4 cardiac procedures. Significant comorbidities before pregnancy were observed in 34% of patients, including obesity (*n* = 5; 15%), diabetes (*n* = 1; 3%), lung disease (*n* = 7; 21%), neurological condition (*n* = 3; 9%), haematological disorder (*n* = 9; 27%), or infection (*n* = 5; 15%).

Nearly all patients had no symptoms of heart failure before pregnancy, with a NYHA functional class I in 96% (*n* = 75) of the cohort and a normal echocardiography cardiac function in 93% of cases (*n* = 76). Seven (8%) patients had pulmonary hypertension (*Table1*).

Maternal cardiovascular events

No death was reported in the study. However, maternal cardiovascular events occurred in 30 (29%) pregnancies, of which 25 (25%) occurred during pregnancy and 12 (12%) in the 3 months postpartum period. The most frequent cardiovascular events were the alteration of the systemic ventricle ejection fraction, the systemic ventricular dilation, the increase in the left outflow tract obstacle, the increase in aortic valve regurgitation, the increase in pulmonary hypertension, or the occurrence of arrhythmia (atrial fibrillation and junctional tachycardia) (*Table 1*).

Table I Population characteristics

Population characteristics			
Number of patients			65
Number of pregnancies			104
Maternal age at delivery			29 ± 6 years
Gestational age at delivery			38 weeks ± 3 days
Number of pregnancies per patient		1	27 (42)
		2	25 (38)
		≥3	13 (20)
Type of CHD[a]	Anomalies of the atria and interatrial communications		7 (11)
	Anomalies of the atrioventricular junctions and valves		7 (11)
	Complex anomalies of the atrioventricular connections		2 (3)
	Functionally univentricular hearts		3 (5)
	Ventricular septal defects		8 (12)
	Transposition of the great arteries		3 (5)
	Tetralogy of Fallot, truncus arteriosus, pulmonary atresia, double outlet right ventricle		12 (18)
	Aortic valve stenosis, Shone syndrome		7 (11)
	Pulmonary valve stenosis		6 (9)
	Anomalies of the extra-pericardial arterial trunks		10 (15)
Number of cardiac surgical procedures (before pregnancy)		0	39 (38)
		1	41 (40)
		≥2	23 (22)
Cardiac status (before pregnancy)	Altered systemic ventricle ejection fraction		5 (6)
	Right ventricle systolic hypertension		6 (7)
	Intracardiac history		73 (71)
	Aortic dilation		7 (8)
	Arterial hypertension		2 (2)
	Pulmonary hypertension		7 (8)
	Cardiac rhythm disorders		9 (9)
	Cardiac conduction disorders		37 (38)
	Cardiac repolarization disorders		7 (7)
NYHA functional class before pregnancy		I	75 (96)
		II	2 (3)
		III	0 (0)
		IV	1 (1)
Obstetrical data	Amniocentesis		10 (13)
	Nulliparous women		65 (63)
	Twin pregnancy		7 (7)
	Medically assisted procreation		5 (5)
	Premature miscarriage		1 (1)
	Medical termination of pregnancy		4 (4)
	Delivery mode	Spontaneous vaginal delivery	53 (55)
		Triggered vaginal delivery	13 (13)
		Scheduled Caesarean delivery	16 (17)
		Unscheduled Caesarean delivery	15 (15)

Table I *Continued*

Population characteristics			
	Indication for Caesarean delivery	Maternal cardiac complications	1 (3)
		Obstetric complications	11 (35)
		Maternal heart disease	13 (42)
		Foetal complication	4 (13)
		Other	2 (6)
	Indication for scheduled delivery	Maternal cardiac complications	4 (14)
		Obstetric complications	9 (32)
		Maternal heart disease	8 (29)
		Foetal complication	6 (21)
		Other	1 (4)
Observed maternal cardiovascular complications	Total		30 (29)
	Per-partum observed cardiovascular complications[b]		25 (25)
	Post-partum (<3 months) observed cardiovascular complications[b]		12 (12)

[a]ACC-CHD classification.
[b]Non-exclusive data (some patients may have presented per- and post-partum complications). Values are indicated as mean ± standard deviation or *N* (%).

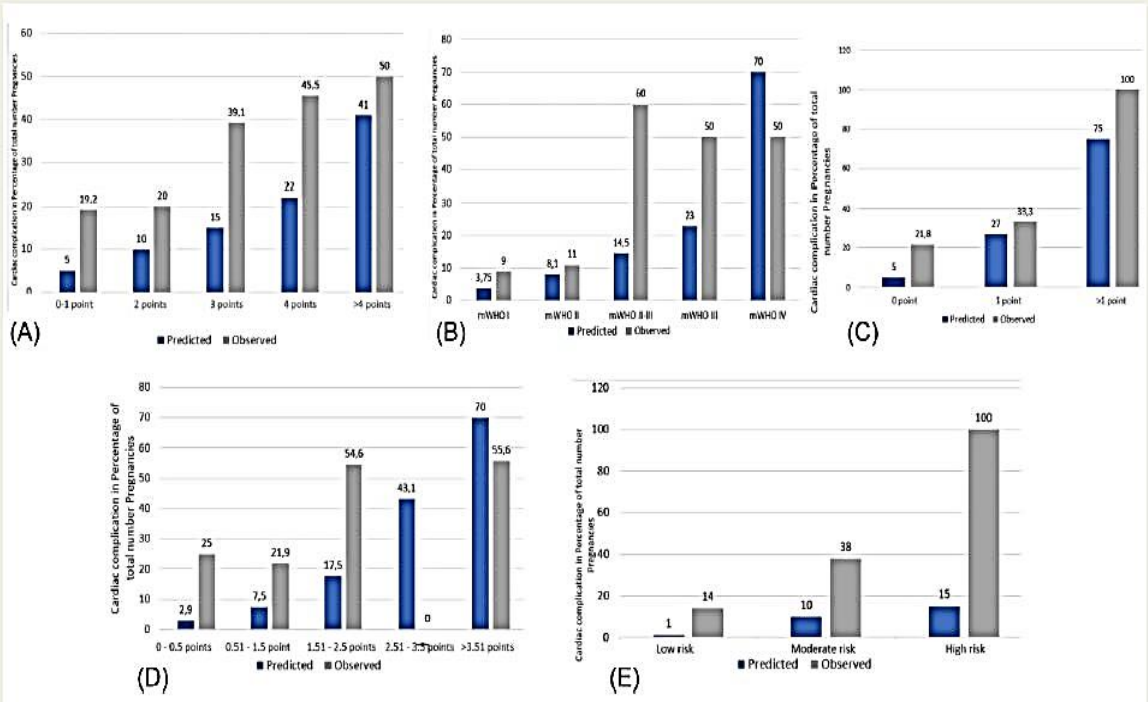


Figure 1 Incidence of maternal cardiac events stratified according to each risk score. (*A*) Incidence of adverse maternal cardiac events (per- and post-partum) stratified according to CARPREG II risk score; (*B*) Incidence of adverse maternal cardiac events (per- and post-partum) stratified according to modified WHO risk score; (*C*) Incidence of adverse maternal cardiac events (per- and post-partum) stratified according to CARPREG risk score; (*D*) Incidence of adverse maternal cardiac events (per- and post-partum) stratified according to ZAHARA risk score; (*E*) Incidence of adverse maternal cardiac events (per- and post-partum) stratified according to HARRIS risk score.

Performance of the cardiovascular pregnancy risk scores

For the five cardiovascular pregnancy risk scores, the observed rate of cardiovascular events was higher than the expected risk (*Figure 1*). In terms of discriminating power for each cardiovascular pregnancy risk score, the AUC values were, in descending order, of 0.75 (0.62–0.88) for mWHO, 0.65 (0.53–0.77) for CARPREG II, 0.60 (0.40–0.80) for Harris, 0.59 (0.47–0.72) for ZAHARA, and 0.58 (0.43–0.73) for CARPREG (*Figure 2*).

The agreement between junior and senior judges was good for all scores but the HARRIS score, with coefficients of correlation of 0.88 (0.81–0.95) for ZAHARA, 0.81 (0.73–0.89) for CARPREG II, 0.80 (0.69–0.91) for CARPREG, 0.78 [95% CI (0.68–0.88)] for mWHO, and 0.09 (0.03–0.16) for HARRIS (*Table 2*).

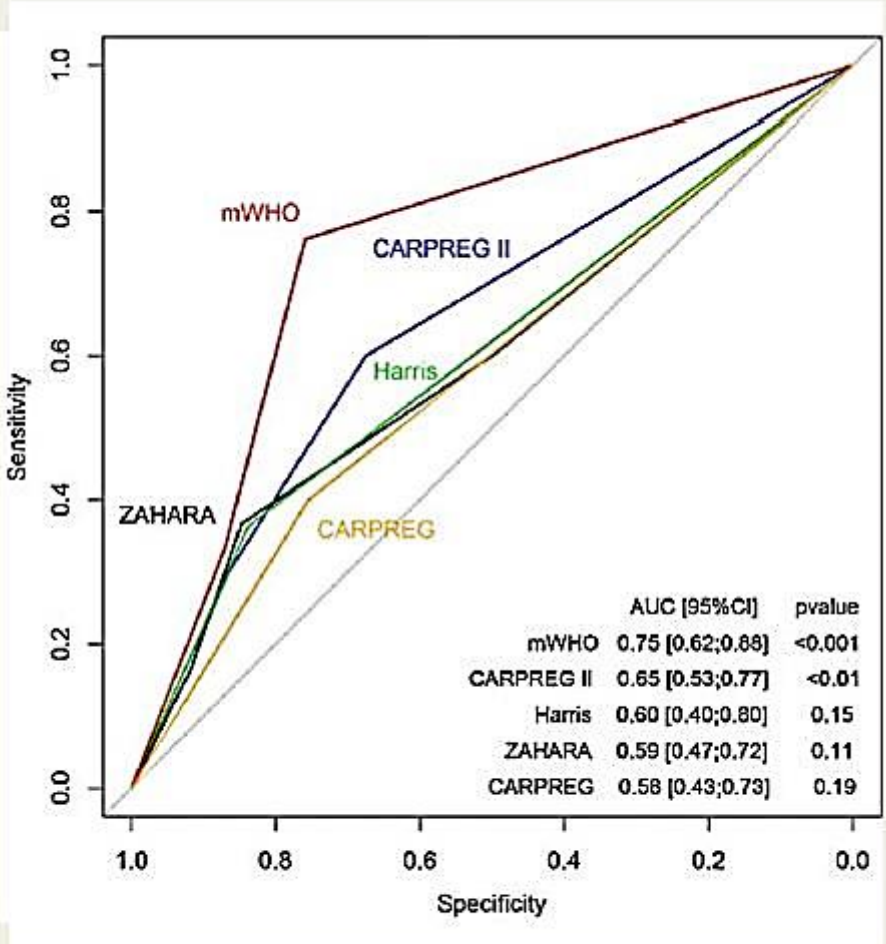


Figure 2 ROC curves of 5 risk estimation methods for predicting maternal cardiac events in patients with congenital heart diseases.

Table 2 Assessment of pregnancy cardiovascular risk scores: agreement between junior and senior judges

Pregnancy cardiovascular risk scores	Weighted Kappa coefficient[a]	(95% CI)	P-value[b]
ZAHARA	0.88	(0.81–0.95)	1.00
CARPREG II	0.81	(0.73–0.89)	1.00
CARPREG	0.80	(0.69–0.91)	0.23
mWHO	0.78	(0.68–0.88)	0.82
HARRIS	0.09	(0.03–0.16)	<0.001

[a] Weighted Kappa coefficient measures the agreement between two judges beyond chance agreement.
[b] When *P*-value > 0.05, the weighted kappa coefficient is significantly different from 0 (i.e. the agreement between judges is significantly greater than chance agreement).

Discussion

From a series of 104 pregnancies in relatively healthy patients with CHD over a decade of multidisciplinary follow-up by our pregnancy heart team, this study describes the cardiac outcomes during pregnancy, delivery, and post-partum period. Overall, no maternal deaths have been reported, and cardiovascular events have affected nearly 30% of pregnancies.

When comparing the five existing cardiovascular pregnancy risk scores, the mWHO classification appeared to provide the most adequate individual assessment of maternal cardiovascular risk, being even more reliable than the specific risk scores developed for CHD.

The mWHO classification is the only one to consider specific heart lesions and clinical cardiac status. In our experience, as in the literature, the mWHO classification seemed easy to use in clinical practice.13,15–17 Furthermore, inter-observer reproducibility between junior and senior physicians was good. The mWHO could therefore be easily used by gynaecologists-obstetricians, cardiologists, or anaesthesiologists in clinical practice. Also, while specialized care is needed for CHD patients during pregnancy, the fact that their risks, even if higher, can be assessed similarly as in other patients, should be reassuring to general obstetricians, potentially increasing patients' access to care.

Moreover, our study found satisfactory discriminating power and good reproducibility of the CARPREG II classification, which is the most recent cardiovascular risk score. These results provide original data on the extrinsic validation of the CARPREG II classification among the CHD population since its first publication in 2018.8,18,19 Although the different CHD subgroups are not included in this classification, the CARPREG II is the only score to take into account the date of the first cardiac assessment during pregnancy, which is a key point for an individualized and adapted management. Indeed, an early, and if possible, preconception evaluation, is essential to optimize haemodynamic and clinical conditions to minimize adverse outcomes.

In this study, we also observed a fairly good cardiovascular tolerance during pregnancy in patients with CHD. Indeed, there was no maternal death, including in patients at higher risk (mWHO IV group). These results are in line with data from larger cohorts, reporting a mortality rate of 0.4% in 372 mWHO IV CHD patients, or even no mortality in 172 patients with CHD.15,16

Also, similarly to our results, recent articles found a low complication and mortality rate in CHD women, but higher compared to a matched control non-CHD population.20,21 All together, these data reinforce the concept of the need for adequate care and follow up of CHD women during pregnancy.

In this study, the observed rate of cardiovascular events was higher than the expected risk, using the five existing cardiovascular pregnancy risk scores. In the recent study from Kim *et al.*, all predictive scores significantly underestimated the actual risk of events in the lowest risk groups of CHD patients.22 Indeed, CHD patients are heterogeneous with variable residual lesions and might be challenging to classify.

We may also hypothesize that important prognostic parameters are missing in the existing pregnancy risk scores. In the ROPAC registry of pregnancy and cardiac disease, the accuracy of the WHO classification was improved when data on pre pregnancy atrial fibrillation and signs of heart failure were added to the classification.15. Similarly, strong surrogates of morbidity in the CHD population, such as aerobic fitness or NT-proBNP, have not been integrated into the existing risk models. Yet, NT-proBNP level >128 pg/mL at 20 weeks of gestation has been considered as an independent risk predictor of cardiovascular events during pregnancy in women with CHD.23 Moreover, aerobic fitness assessed by cardiopulmonary exercise test provides a more objective quantification of the functional status than the NYHA classification.24,25 Also, pregnancy risk assessment for CHD patients based on physiological classes26 may be more accurate compared to the use of anatomic classifications, being more associated with adverse outcomes.27

Finally, none of the five existing risk scores have integrated maternal and foetal outcomes. Indeed, maternal cardiac disease is associated with an increased risk of foetal complications, such as spontaneous abortion, prematurity, intrauterine growth retardation, recurrence of congenital cardiac malformations, and foetal loss.28–30

Altogether, the results of this study highlight that, on the one hand, caregivers can rely on some of the current models for pregnancy risk assessment in CHD, and on the other hand, the development of dedicated scores for CHD integrating physiological and anatomic classification may be useful. In the near future, the challenge for risk models will also be to integrate reliable prognostic parameters, including both foetal and maternal outcomes, in order to provide a comprehensive and global assessment of the pregnancy risk in patients with CHD.31,32

Study limitation

The results may be limited by the study sample size, the absence of data on pregnancies <20 weeks of gestation, and the heterogeneity of structural heart diseases. Nevertheless, this cohort is representative of patients followed in a tertiary-care CHD centre. Information bias due to patient misclassification has been limited by the blind scoring involving three investigators. In addition, patients at low or negligible risk may not have been referred to a regional centre, and those deemed at the highest risk may have been counselled against pregnancy. Lastly, the events reported were predominantly diagnostic signs, rather than clinical symptoms, because different scores had significantly different measures of clinical signs, without necessarily changes in end-point outcomes.

Conclusion

Among the five existing pregnancy cardiovascular risk scores, this study found that the modified WHO classification appeared to better predict cardiovascular outcome in pregnant women with CHD than the four other existing risk scores. Cardiovascular tolerance of pregnancy in patients with CHD was good and no maternal death occurred during pregnancy and in post-partum. Nevertheless, all five scores underestimated the actual observed rate of cardiovascular events. This result may be of interest for the 'pregnancy heart team', as it may help to standardize risk in CHD patients, who need adequate pre-pregnancy prediction of maternal cardiovascular and offspring risk to optimize counselling and management.

Funding

None.

Conflict of Interest:

None declared.

Data availability statement

The data underlying this article will be shared on reasonable request with the corresponding author.

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