Pregnancy in women with congenital heart disease: New insights into neonatal risk prediction

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ABSTRACT

Background Advances in managing adult congenital heart disease (ACHD) have led to an increased number of women with CHD reaching childbearing age. This demographic shift underscores the need for improved understanding and prediction of complications during pregnancy in this specific ACHD population. Despite progress in maternal cardiac risk assessment, the prediction of neonatal outcomes for ACHD pregnancies remains underdeveloped. Therefore, the aims of this study are to assess neonatal outcomes in a CHD women population, to identify their predictive factors and to propose a new risk score for predicting neonatal complications.

Methods This registry study included all women born between 1975 and 1996 diagnosed with ACHD who underwent at least one cardiology consultation for ACHD in Cliniques Universitaires Saint-Luc. A multivariate analysis was performed to identify predictors of neonatal complications and these were incorporated into a new risk index. Its validity was assessed using bootstrap method. This score was then compared with scores adapted from the ZAHARA and CARPREG studies for offspring events prediction.

Results Analysis of 491 pregnancies revealed 31.4% of neonatal complications. Four significant predictors of adverse neonatal outcomes were identified: cardiac treatment during pregnancy (OR 14.8, 95%CI [3.4-66]), hypertensive disorders of pregnancy (OR 11.4, 95%CI [3.4-39.0]), smoking during pregnancy (OR 10.6, 95%CI [2.8-40.6]), and pre-pregnancy BMI <18.5 kg/m^2 (OR 6.5, 95%CI [2.5-16.5]). The risk model demonstrated an AUC of 0.70 (95%CI [0.65-0.75]), which remained stable after bootstrap validation. This model significantly outperformed the scores adapted from ZAHARA and CARPREG data. Based on the regression coefficients, a risk score was subsequently developed comprising five risk categories.

Conclusions One third of ACHD pregnancies are complicated by poor neonatal outcome. These complications are determined by four independent factors relating to the cardiac and non-cardiac status of the patients, which have been incorporated into a risk score. Our study is one of the first to propose a predictive risk score of neonatal outcomes in ACHD pregancies, and paves the way for other validation and confirmation studies. (Am Heart J 2024;273:148–158.)

Abbreviations

ACHD	Adult Congenital Heart Disease
ASD	Atrial Septal Defect
AUC	Area Under the Curve
BMI	Body Mass Index
CHD	Congenital Heart Disease
CIs	Confidence Intervals
ESC	European Society of Cardiology
GLMM	Generalized Linear Mixed Model
HDPs	Hypertensive Disorders of Pregnancy
mWHO	Modified World Health Organization

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NYHA	New York Heart Association
ORs	Odds Ratios
PDA	Patent Ductus Arteriosus
PIH	Pregnancy-Induced Hypertension
ROC	Receiver Operating Characteristic
SGA	Small-for-Gestational-Age
TGA	Transposition of Great Arteries
TOF	Tetralogy of Fallot
VSD	Ventricular Septal Defect

Background

Over the past few decades, advances in cardiac surgery and catheterization have improved survival and quality of life of patients with Congenital Heart Disease (CHD), thereby increasing the population of women of childbearing age.[1] Nowadays, women with CHD expect to lead a life that conforms to the norm, including a desire for pregnancy and motherhood. However, it is well established that pregnancy in this population carries risks in terms of maternal cardiac complications, as well as obstetric and neonatal risks.[2–4] Identifying patients at heightened risk for complications during pregnancy is therefore essential for their optimal management.

While recent research has shed light on predicting maternal cardiac risks,[5-8] there remains a significant gap in understanding and predicting obstetric and neonatal events. To date, unlike the advances in maternal cardiac risk assessment, no validated scoring system exists for predicting neonatal complications specifically tailored to the CHD population. Indeed, while some neonatal predictors are noted in the literature, the most prominent studies in this area do not specifically focus on the CHD population.[5,9] The absence of such a specialized prediction tool clearly highlights an essential area of antenatal care for CHD that remains unresolved.

In this context, the aims of this study are[1] to assess neonatal outcomes in a CHD women population,[2] to identify their predictive factors and[3] to propose a new risk score for predicting neonatal complications.

Material and methods

No extramural funding was used to support this work. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting, and editing of the paper and its final contents.

Study design and population

This registry study included all women born between January 1, 1975, and December 31, 1996, diagnosed with CHD, who underwent at least one Adult Congenital Heart Disease (ACHD) cardiology consultation at the Cliniques Universitaires Saint-Luc. Specific lesions were excluded from this study for targeted reasons. Patients with isolated aortic coarctation were excluded to maintain our focus on intracardiac congenital heart disease itself rather than isolated vascular pathology. Likewise, isolated valvular pathologies, such as mitral or aortic valve dysplasia, were excluded due to uncertainties in their purely congenital origins. Additionally, conditions like triatrial heart were excluded because of their extreme rarity. The study encompasses consecutive successful pregnancies documented in the registry from 1995 to 2022, excluding miscarriages and elective abortions before 20 weeks gestation.

Baseline demographic and clinical data, including parity, type and complexity of cardiac lesion, history of cardiac interventions, comorbid conditions, functional classification according to the New York Heart Association (NYHA), and pre-pregnancy Body Mass Index (BMI), were extracted from electronic medical records. Detailed data related to each pregnancy, such as maternal age at the time of pregnancy, monitoring location, use of cardiac or non-cardiac medication, tobacco and/or alcohol consumption, and specifics about delivery and newborn health, were also collected. Additionally, neonatal outcomes were reported. Neonatal outcomes included preterm birth (<37 weeks' gestation), small-for-gestational-age (SGA) (weight <10th percentile), acute fetal distress, newborn respiratory distress and offspring mortality (>20 weeks of gestation untill <28 days after birth). Recurrence of CHD in offspring was separately evaluated. Data were extracted by reviewing electronic medical records and communicating with the referring physician if necessary. Informed consent for the use of medical records for research purposes was obtained in accordance with institutional review board guidelines.

Risk classification

Neonatal risk was calculated based on previously reported predictors from the CARPREG and ZAHARA studies,[5,8] with points assigned to these predictors according to their odds ratios (ORs). While the original CARPREG and ZAHARA studies did not establish a formal scoring system for neoatal outcomes, their data were adapted into a scoring format for use in our Receiver Operating Characteristic (ROC) curve analysis. The methodology is explained in the Data Analysis section.

Data analysis

All analyses were conducted using R (R Core Team, 2020) and RStudio (Rstudio Team, 2020). Continuous variables were presented as mean values ± 1 standard deviation (SD), while categorical variables were expressed as absolute numbers and percentages.

Because some women underwent more than one pregnancy, these repeated events within the same patient were not independent of each other. Therefore, to identify predictors associated with neonatal outcomes, we

applied a Generalized Linear Mixed Model (GLMM) using a binary response variable (occurrence of neonatal outcomes, yes *vs*. no) as the dependent variable. In the univariate analysis, variables reaching a significance level of $P < .1$ were considered for inclusion in the multivariate analysis. The multivariate analysis results, both unadjusted and adjusted, were expressed as ORs with 95% confidence intervals (CIs). Only variables statistically significant at $P < .05$ in the multivariate analysis were used to develop the final risk score. To evaluate the robustness and accuracy of the developed risk model, we performed bootstrapping with 1,000 samples, drawn with replacement. The average area under the curve (AUC) after bootstrapping and its 95%CI were reported. Subsequently, a risk score was developed based on this model, assigning points to each predictor according to their respective regression coefficients.

Finally, we compared this newly developed risk score with the scores derived from the ZAHARA and CARPREG studies. These were established using the methodology applied in the manuscript by Balci et al[10]. To adapt the predictors of the neonatal risk from the ZAHARA and CARPREG studies into a practical scoring system for neonatal risk prediction, we assigned points to each predictor based on the logarithm of the odds ratios (log-odds) reported in these studies (Tables A1 and A2) . Multiple ROC curves were drawn by plotting the sensitivity against (1-the specificity) for each offspring risk score. The AUC with its 95%CI was calculated to evaluate the most discriminant score. A two-tailed *P*-value of <.05 was considered statistically significant.

Results

Pre-pregnancy baseline data

Among women born between 1975 and 1996, 725 were eligible for inclusion. Of these, 287 were excluded because of nulliparity, 35 because of incomplete pregnancy (miscarriage <20 weeks [n = 29] or elective abortion [n = 6]) and 113 patients were excluded based on cardiac lesions, resulting in a final cohort of 290 patients. For the present analysis, the data of their 491 pregnancies were used (Figure 1 – Flow chart).

The distribution of CHD lesions among patients are shown in Figure 2: (un)corrected atrial septal defect (ASD, 28%), (un)corrected ventricular septal defect (VSD, 19% including 3% associated with aortic coarctation), tetralogy of Fallot (TOF, 14%), pulmonary valve stenosis (12%, including 1 with >50 mmHg obstruction), atrial or arterial corrected complete transposition of great arteries (TGA, 9%, 2.6% atrial correction), atrioventricular septal defect (7%), isolated patent ductus arteriosus (PDA, 5%), (un)corrected partial anomalous of pulmonary vein return (3%). ASD, VSD, and TOF together accounted for over 50% of the CHD lesions. The least common CHDs were Ebstein's disease (1%), double outlet right ventricle (1%), and univentricular heart (0.7%).

All baseline data by pregnancy are reported in Table 1. Of the 491 pregnancies, more than half (56.6%) were in women with mild CHD, 35.8% were in women with moderate CHD, and 7.5% in women with severe CHD according to the European Society of Cardiology (ESC) classifi-

Figure 1. Flow chart of the study.

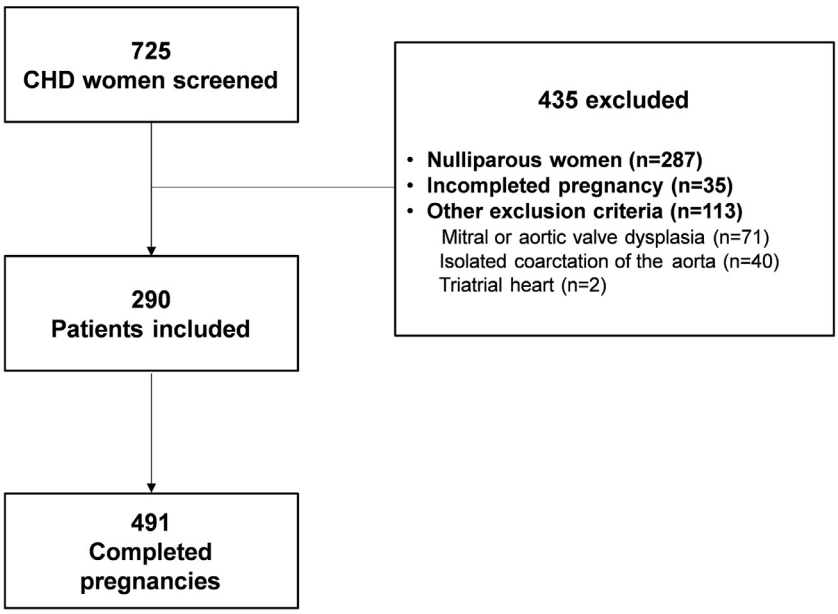


Figure 2. Distribution of Congenital Heart Disease lesions (n = 290). ASD, Atrial Septal Defect; AVSD, Atrioventricular Septal defect; CoA, Coarctation of the Aorta; PA, Pulmonary Atresia; PAPVR, Partial Anomalous Pulmonary Venous Return; PDA, Patent Ductus Arteriousus; PS, Pulmonary Stenosis; TGA, Transposition of Great Arteries; TOF, Tetralogy Of Fallot; VSD, Ventricular Septal Defect.

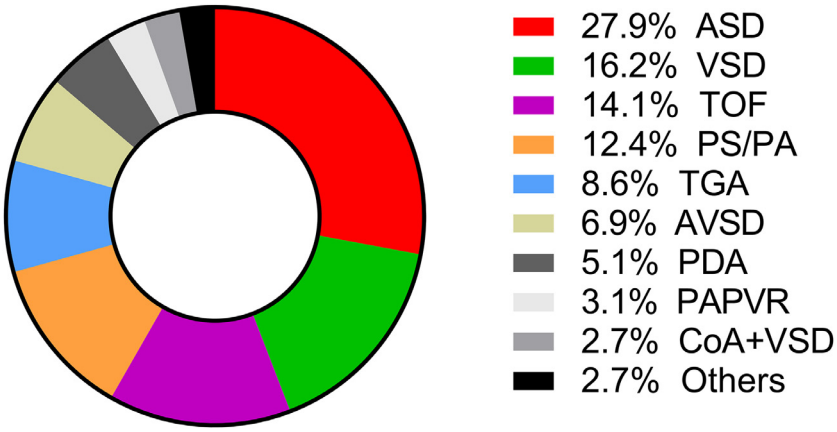


Table 1. Pre-pregnancy baseline data

	All pregnancies *N = 491*
CHD characteristics, n (%)	
ESC complexity classification	
• Mild	278 (56.6)
• Moderate	176 (35.8)
• Severe	37 (7.5)
Cyanotic CHD	132 (26.9)
Unrepaired CHD	75 (15.3)
Past medical history, n (%)	
Arrhythmia	49 (9.9)
Heart failure	3 (0.6)
Pacemaker/defibrillator	15 (3.0)
Endocarditis	11 (2.2)
Mechanical valve	4 (0.8)
Hypertension	41 (8.3)
Ischemic heart disease	0
Cerebrovascular accident	10 (2.0)
Smoking history	156 (31.8)
Pre-pregnancy clinical data	
BMI, kg/m²	23.4 ± 4.43
Obesity, n (%)	30 (6.1)
Underweight, n (%)	49 (10)
NYHA class	
• I	474 (96.6)
• II	16 (3.2)
• III	1 (0.2)
mWHO class	
• I	227 (46.2)
• II	234 (47.7)
• III	30 (6.1)

BMI, Body Mass Index; CHD, Congenital Heart Disease; ESC, European Society of Cardiology; NYHA, New York Heart Association; mWHO, Modified World Health Organization.

cation.[11] Cyanotic CHD was present in almost one-third of pregnancies, and unrepaired CHD in 15.3%. All cases of cyanotic CHD had been repaired prior to pregnancy.

Mean body mass index (BMI) before pregnancy was 23.4 ± 4.43 kg/m², pre-pregnancy obesity (BMI >30 kg/m²) and underweight (BMI <18.5 kg/m²) affected respectively 6.1% and 10% of cases.

Pregnancy outcomes

Mean maternal age at the time of pregnancy was 27.9 ± 4.5 years.

Cardiac drugs were used in 6.1% of pregnancies (Table 2). There was a significant difference in cardiac disease complexity between groups taking cardiac medication during pregnancy and those who did not: patients taking cardiac drugs had more complex heart disease (33.3% vs. 5.9% ESC class III, $P < .001$) (Table A3).

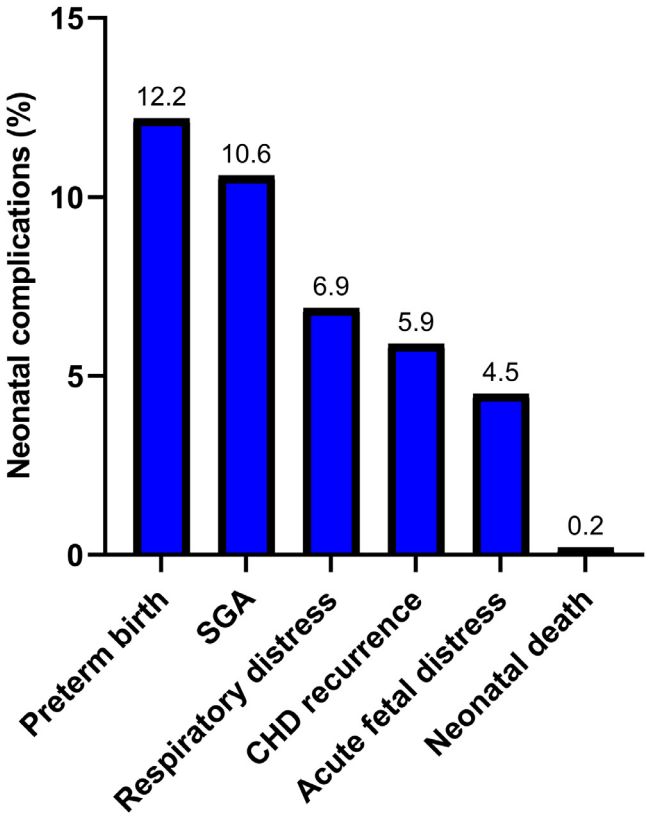
Smoking was noted in 5.5%. Thirty-three (6.7%) of pregnancies were complicated by hypertensive disorders of pregnancy (HDPs). Other exposures and risk factors during pregnancy are reported in Table 2. Twin pregnancies accounted for 2% of all pregnancies (n = 10).

Mean gestational age at delivery was 38.4 ± 2.3 weeks and average baby's weight was 3.12 ± 0.58 kg. Offspring complications occurred in 156 pregnancies (31.7%). Preterm birth and SGA were the most encountered complications, affecting 12.2% and 10.6% of pregnancies respectively. The CHD recurrence rate was 5.9%. There was only one case of neonatal death (Figure 3).

Predictors of neonatal outcomes and risk scores

The results of the univariable logistic regression for the fetal and neonatal complications are displayed in Table 3. The multivariate logistic mixed-effects model

Figure 3. Neonatal complications rates during pregnancy (expressed as % of the total number of completed pregnancies). CHD, congenital heart disease; SGA, small for gestational age.



identified 4 variables to predict adverse neonatal outcomes: cardiac treatment during pregnancy, hypertensive disorders of pregnancy, smoking during pregnancy, and a pre-pregnancy BMI <18.5 kg/m². Table 4 displays the 4 predictors and their ORs before and after adjustment for cardiac and obstetric risk factors. As 100% of twin pregnancies experienced neonatal complications, there were not included in the risk model. To facilitate clinical application, we converted the odds ratios of these predictors into weighted scores. This risk index is divided in five categories according the sum of the points for the indexed pregnancy: 0 points (217 pregnancies), 1 points (191 pregnancies), 2 points (34 pregnancies), 3 points (28 pregnancies) and ≥4 points (21 pregnancies). The predicted risk for offspring according the point score was 15% when 0 point, 30% when 1 point, 45% when 2 points, 60% when 3 points and 85% when ≥4 points.

The ROC curve (Figure 4) of the CARPREG and ZAHARA neonatal risk scores reveals that these scores have a poor predictive performance in our study population (AUC of 0.53, $P = .29$ and AUC of 0.53, $P = .32$ respectively). Our model achieved an AUC of 0.70 (95%CI 0.65-0.75) for predicting neonatal outcomes across the entire cohort (Figure 4). Figure 5 reveals that 11% of pregnancies (n = 53) were under-classified by the CARPREG score and 15% (n = 71) by the ZAHARA score as being lower risk than identified by our scoring system.

The mean AUC of our risk model, as obtained in the 1,000 bootstrap samples, remained stable at 0.71 (95%CI 0.65-0.77). Figure 6 displays the new risk score developed based on this model, along with the corresponding neonatal risk during pregnancy.

Discussion

This study is one of the first to look specifically at the neonatal risk in pregnancies of women with congenital heart disease. This manuscript highlights the following points:

1. One third of ACHD pregnancies are complicated by poor neonatal outcome.

Table 2. General pregnancy data

	All pregnancies *N = 491*
Place of pregnancy follow-up, n (%)	
Primary/secondary care center	337 (68.6)
Tertiary care center	154 (31.4)
Conception method, n (%)	
Natural Conception	463 (94.1)
In vitro fertilization	28 (5.7)
Treatments during pregnancy, n (%)	
Any cardiac drugs	30 (6.1)
• Beta blockers	6 (1.2)
• Diuretics	12 (2.4)
• Aspirin	9 (1.8)
• Heparin/VKA	3 (0.6)
Other drugs	
• Progesterone	75 (15.3)
• Corticosteroids	33 (6.7)
• Antibiotics	46 (9.4)
• Insulin	15 (3.0)
Exposures and pregnancy risk factors, n (%)	
Smoking during pregnancy	27 (5.5)
Alcohol use during pregnancy	5 (1.0)
Weight gain during pregnancy, kg	12.9 ± 7.4
Gestational diabetes	51 (10.4)
Hypertensive disorders of pregnancy*	33 (6.7)
Primiparity	290 (59.1)
Type of delivery, n (%)	
Caesarean section	125 (25.4)
Vaginal delivery	366 (74.6)

*Presence of pregnancy induced hypertension (PIH; new-onset hypertension with blood pressure >140 mmHg systolic or >90 mmHg diastolic without proteinuria after 20 weeks of gestation), preeclampsia (PIH with ≥0.3 g protein in a 24-hour urine sample), or eclampsia (preeclampsia with grand mal seizures). VKA, Vitamin K Antagonist.

Table 3. Univariable model for neonatal outcomes prediction

	OR (95%CI)	*P*-value
mWHO class > II	3.2 (1.0-11.4)	.05
ESC class III	2.5 (0.8-7.7)	.088
Single or right systemic ventricle	3.5 (1.1-12.9)	**.045**
Pre-pregnancy BMI < 18.5 kg/m²	4.7 (2.1-11.9)	**.0003**
Prior cardiac events or arrhythmia	2.8 (1.3-6.8)	**.0132**
Cardiac treatment during pregnancy	16.3 (5.1-69.4)	**<.0001**
Hypertensive disorders of pregnancy	11.9 (3.9-45.6)	**<.0001**
Smoking during pregnancy	6.5 (1.9-27.1)	**.004**

BMI, Body Mass Index; CI, Confidence Interval; ESC, European Society of Cardiology; mWHO, Modified World Health Organization; OR, Odds Ratio.

2. All twin pregnancies experienced neonatal complications. Four other risk factors have been identified as having a poor neonatal prognosis: cardiac treatment during pregnancy, hypertensive disorders of pregnancy, smoking during pregnancy, and a pre-pregnancy BMI < 18.5 kg/m.
3. The newly developed neonatal risk score provides a reliable prediction of neonatal outcome.

Neonatal complications

In our series, fetal and neonatal complications occurred in 31.7% of pregnancies. This is comparable to the series of Khairy et al., Chu et al., and Balci et al. where neonatal complications rate among CHD women was 27.8%, 29.2% and 37.3% respectively.[10,12,13] The rate of neonatal complications is significantly higher than in the general population,[14] which was estimated at 7% in the study by Siu et al.[9] Consistent with previous studies, preterm birth was the most common event, followed by SGA.[5,8,9,12,13,15,16] The CHD recurrence rate of 5.9% in the offspring was also similar to the rates previously reported in the literature.[9,10,17-21]

We identified four predictors of adverse neonatal outcomes : hypertensive disorders during pregnancy, use of cardiac treatment during pregnancy, smoking during pregnancy, and low maternal BMI (<18.5 kg/m²) before pregnancy. Moreover, neonatal complications occurred in 100% of twin pregnancies.

Smoking during pregnancy and twin pregnancies are neonatal prognostic factors that were also found in the CAREPREG and ZAHARA studies, but also in the series by Siu et al.[5,9] In their review, D. Morales-Pietro et al. reported the harmful effect of tobacco on placental function and fetal development by impacting placental vascularization and metabolism.[22] In our series, 5.5% of the patients actively smoked during pregnancy. Ideally, this figure should be close to zero, in particular through pre-pregnancy counselling.

In our study, all multiple pregnancies resulted in complications in the offspring, rendering this factor non-includable in our model. According to the meta-analysis of Roman A. et al, twins represent 3.2% of all live births. However, they account for 20.0% of all preterm deliveries, with 60.0% and 10.7% of twins delivered before 37 and 32 weeks' gestation, respectively.[23] This is likely because multifetal pregnancies exert a greater load on the cardiovascular system, evidenced in part by an increased cardiac output and reduced total vascular resistance.[24] In the study by van Hagen et al., multiple pregnancies were the most powerful predictor of neonatal events.[25] Effectively, the risk of twin pregnancies is added to the neonatal risk associated with maternal CHD, which explains the high incidence of complications in multiple pregnancies.

We found that the use of cardiac treatment during pregnancy, including diuretics, beta-blockers, aspirin or anticoagulants, was also independently associated with adverse neonatal complications. In the ROPAC registry, 28% of patients took cardiac medications during pregnancy, compared with just 2% in the control population.[26] Moreover, as observed in our study, patients requiring medications during pregnancy tend have more severe cardiac conditions.[27] On the other hand, similar

Table 4. Multivariable model for neonatal outcomes prediction

	OR (95%CI)	*P*-value	Adjusted OR (95%CI)	*P*-value
Cardiac treatment during pregnancy	14.9 (4.6-64.3)	**<.0001**	14.8 (3.4-66)	**.0003**
Hypertensive disorders of pregnancy	10.4 (3.4-39.5)	**.0001**	11.4 (3.4-39.0)	**<.0001**
Smoking during pregnancy	10.3 (3.0-44.9)	**.0005**	10.6 (2.8-40.6)	**.0005**
Pre-pregnancy BMI < 18.5 kg/m²	6.2 (2.6-16.5)	**<.0001**	6.5 (2.5-16.5)	**<.0001**
Primiparity	-	-	1.4 (0.8-2.4)	.195
In vitro fertilization	-	-	0.9 (0.3-3.5)	.965
Gestational diabetes	-	-	1.0 (0.4-2.6)	.979
ESC class III	-	-	1.5 (0.3-7.5)	.629
mWHO class > II	-	-	0.7 (0.1-4.6)	.703
Cardiac events during pregnancy	-	-	1.3 (0.2-6.7)	.774

BMI, body mass index; CI, confidence interval; ESC, European Society of Cardiology; mWHO, Modified World Health Organization; OR, odds ratio; OR, odds ratio.

Figure 4. Receiver operating characteristics curves of neonatal outcomes for the different offspring risk models.

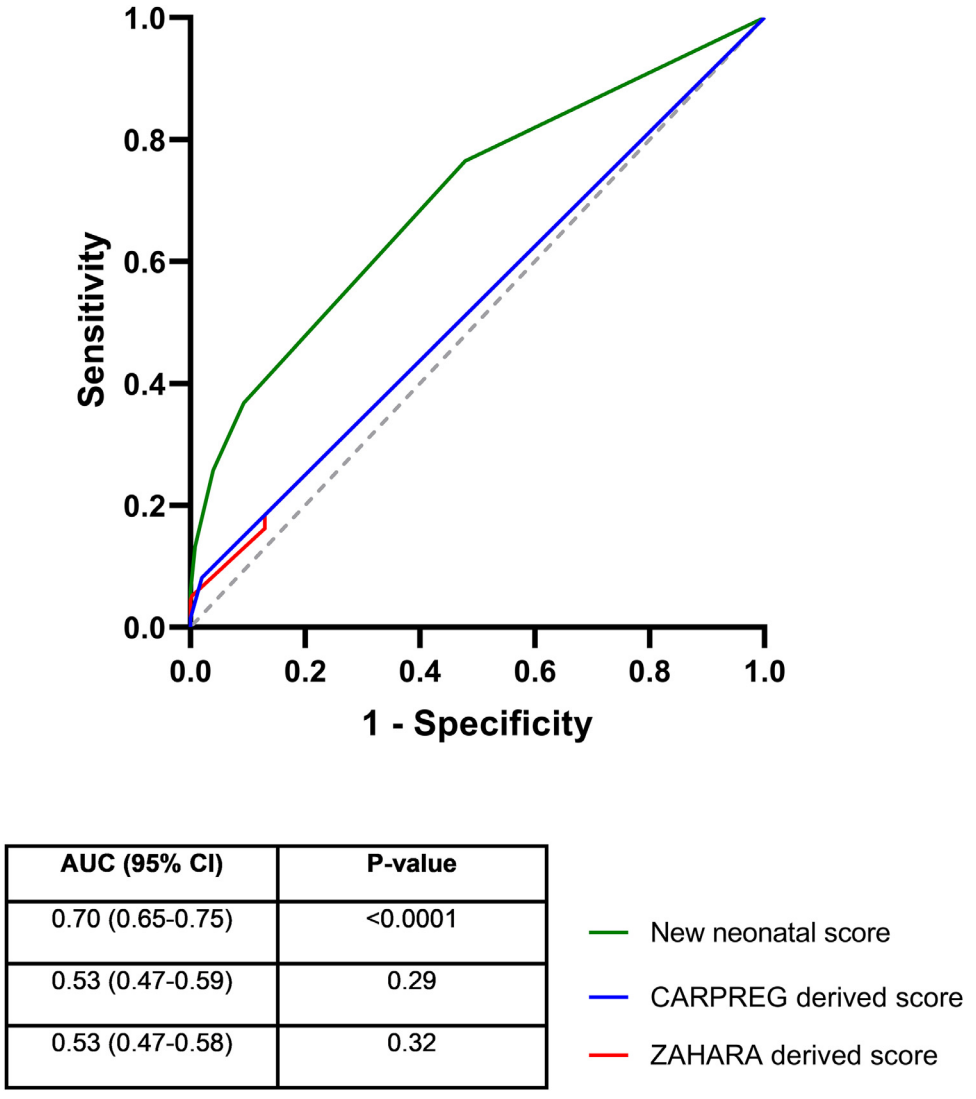


Figure 5. Comparison of risk stratification: new score vs. established CARPREG and ZAHARA offspring scores.

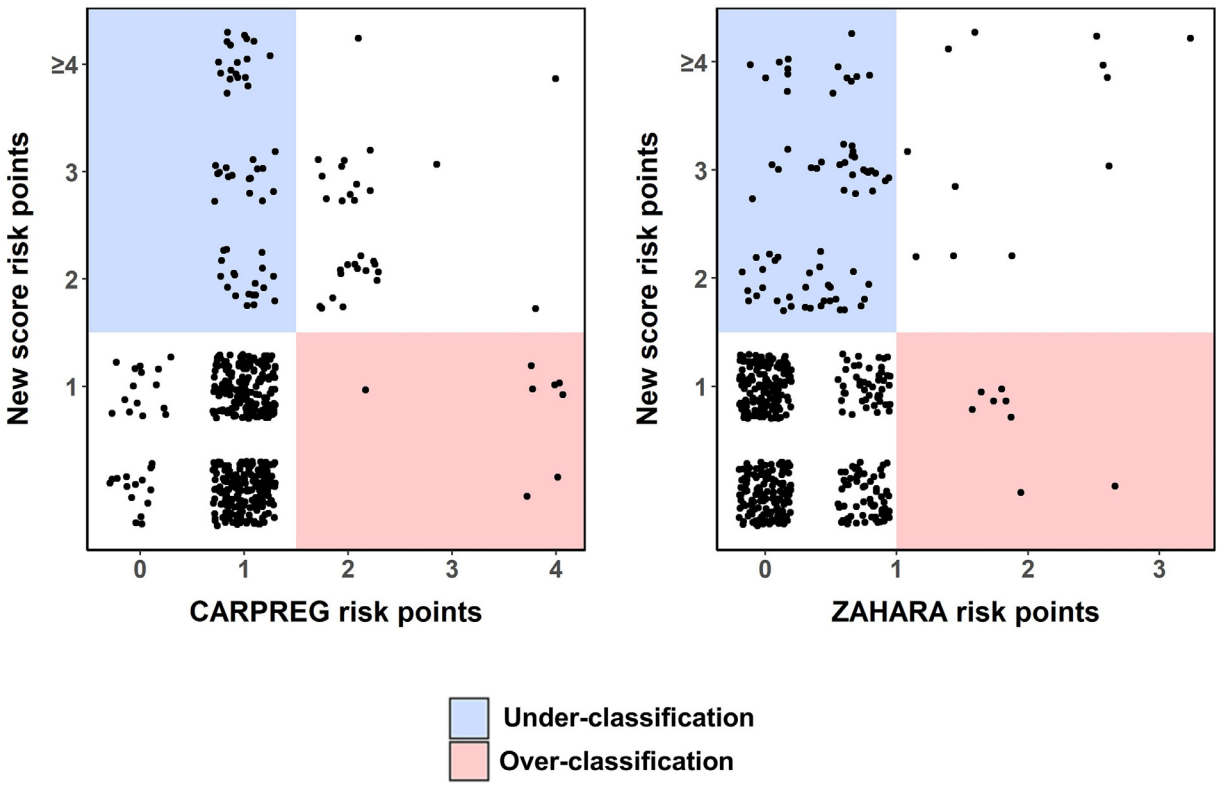
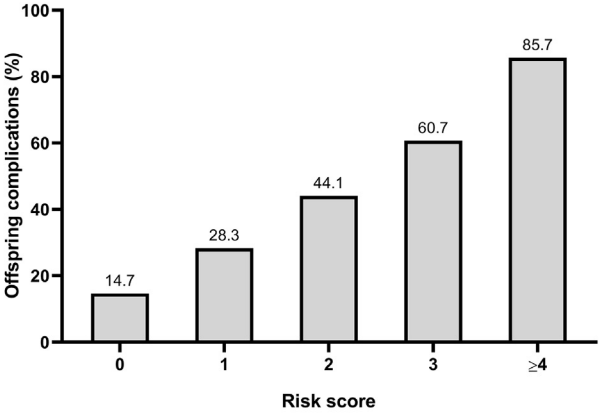


Figure 6. The new risk score for neonatal outcomes in women with congenital heart disease and complication rates in offspring according to risk category. [1]Cardiac treatment during pregnancy included diuretics, beta-blockers, aspirin and anticoagulants.

PREDICTORS	POINTS
Cardiac treatment during pregnancy[1]	3
Hypertensive disorders of pregnancy	2
Smoking during pregnancy	2
Pre-pregnancy BMI < 18.5 kg/m²	1



Number of pregnancies at risk	217	191	34	28	21
Percentage of total population	44.2	38.9	6.9	5.7	4.3

to our study, the association between the use of cardiac drugs and increased neonatal adverse events is also reported by these authors as well as Drenthen et al. and Siu et al.[5,8] Khairy et al. showed that both anti-platelet therapy and anti-arrhythmic cardiac medication were univariate predictors for spontaneous abortion.[12] However, this association was also found even after adjustment for cardiac and obstetric parameters.[27] Similarly, in our study, after adjustment, cardiac medication during pregnancy remained an independent predictor of neonatal complications. However, these results also underline the need for dedicated studies to discriminate the effect of cardiac pathology requiring medication vs. the medication itself on neonatal outcome.

Our study is the first to identify pre-pregnancy BMI as a predictor of fetal events, suggesting that a lower BMI may increase the risk of adverse offspring events. Evidence exists linking maternal underweight to low birth weight in the general population, but this association had not previously been demonstrated within the CHD population.[28] Notably, in our cohort, mothers who were underweight prior to pregnancy (BMI $\leq$18.5 kg/m^2) experienced a 25% SGA babies rate, compared to only 10% among those with a pre-pregnancy BMI greater than 18.5 kg/m^2.

CARPREG and ZAHARA risk score

The ZAHARA and CARPREG registries have made it possible to establish prediction scores for neonatal events. Our study has shown that these scores are poorly adapted to the current population of CHD patients. Indeed, the predictive power is very low since the AUC of the ROC curve was <0.6 for both scores. These results had already been noted by Balci A et al who showed that all the offspring risk models performed insufficiently in predicting fetal events (AUC < 0.6).[10]

The lack of performance of these two scores can firstly be attributed to differences between our cohort and the populations of these registries. Firstly, our cohort exclusively included patients with CHD, without including other types of heart disease present in the CARPREG registry. Secondly, based on their populations, the ZAHARA and CARPREG registries identified predictive factors such as NYHA class III/IV, cyanosis, left heart obstruction, and the presence of a mechanical valve as important risk factors for neonatal complications. However, most of these predictive factors were absent in our population, with only one case of NYHA III and four cases of mechanical valves. Furthermore, as shown in Figure 5, our findings indicate that the ZAHARA and CARPREG scores tend to under classify the neonatal risk more often than they overestimate it, when compared to our own score. This difference between the populations may explain not only the inadequacy of the ZAHARA and CARPREG scores for our cohort, but also the mismatch in scores observed for certain segments of our population, as shown in Figure 5.

Finally, these discrepancies between our cohort population and that of the registries could also be due to our more contemporary patient population, since both registries include patients who gave birth up to 20 years ago. Two-thirds of the pregnancies in our study occurred after 2011. Since then, guidelines have advised a prenatal consultation to assess cardiac and neonatal risks and to treat any adverse factors, such as residual lesions.[29] As a result, women are probably entering pregnancy with a lower level of risk than in previous years.

New neonatal risk score

Very interestingly, the factors predictive of neonatal complications included in this score refer to the patient's cardiac status (medications) but also to the non-cardiac status (pre-pregnancy BMI, smoking during pregnancy and hypertensive disorders during pregnancy). However, some of these parameters (very low pre-pregnancy BMI, active smoking and hypertensive disorders) are parameters that are not specific to CHD patients and are likely to be found in a population of women without CHD. Siu et al.[9] showed that most of the risk factors for neonatal complications were similar in patients with heart disease than in the control group. However, and very surprisingly, they demonstrated that the deleterious effects of maternal heart disease on neonatal outcomes were amplified by the presence of obstetric risk factors, such as age, multiple gestation, maternal smoking during pregnancy and arterial hypertension, concomitant with neonatal complications. From a pathophysiological point of view, this interaction could be explained by placental underperfusion, particularly influenced by an impaired microcirculation, in top of an impaired cardiac output linked to the congenital cardiopathy. Indeed, maternal smoking and hypertensive disorders of pregnancy lead to endothelial dysfunction and disrupt the normal development of placental microcirculation.[30] In patients without heart disease, this microcirculatory impairment has already been associated with adverse fetal outcome.[31-33]

Study limitations

This study has limitations that should be acknowledged.

This is a retrospective study. Despite the completeness of our medical records searches, some data were missing and therefore could not be included in the model calculations. These were mainly pre-pregnancy hemodynamic parameters.

Patients with a risk score of 0 had a 15% incidence of neonatal complications. In this sub-group, our model could therefore be refined to define neonatal outcome more precisely.

Moreover, although internal validation has strengthened confidence in the reliability of our score, external

validation is crucial for assessing its applicability and generalizability to larger populations.

Finally, the majority of data collected in this study were mostly clinical. Subclinical data, such as specific blood biomarkers, could potentially improve the accuracy of our predictive model and provide a better understanding of the underlying mechanisms involved in these complications.

Conclusion

Pregnancy in CHD women remains a significant medical concern, characterized by a notable incidence (31.7%) of neonatal complications. Four independent predictors of neonatal outcomes were identified (including cardiac treatment during pregnancy, hypertensive disorders of pregnancy, smoking during pregnancy, and low pre-pregnancy BMI) which were included in a risk score.

Pregnancy-related risk must be assessed in terms of both cardiovascular risk and neonatal risk. This assessment must take into account both cardiac and non-cardiac factors. Further studies will be needed to determine the practices needed to improve this prognosis.

Conflict of interest

The authors have indicated they have no conflicts of interest relevant to this article to disclose.

CRediT authorship contribution statement

Nour Rahnama: Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Nour Ben Jemâa:** Methodology, Data curation. **Arthur Colson:** Data curation. **Agnès Pasquet:** Supervision, Data curation. **Laura Houard de Castro:** Data curation. **Frédéric Debière:** Supervision. **Sophie Pierard:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization.

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Appendix

Table A1. CARPREG derived score for neonatal outcome prediction

Predictor	Risk point (offspring risk)
NYHA functional class III.IV or cyanosis (SpO2 <90%)	1
Left heart obstruction (MVA <2cm², AVA <1,5cm² or PG >30 mmHg)	0.75
Multiple gestation	3
Smoking	1
Heparin/Warfarin during pregnancy	1

MVA, mitral valve area; AVA, aortic valve area; PG, peak gradient.

Table A2. ZAHARA derived score for neonatal outcome prediction

Predictor	Risk point (offspring risk)
Mechanical valve prosthesis	2.5
Cardiac medication before pregnancy	0.75
Cyanotic heart disease (corrected or uncorrected)	0.75
Twin or multiple gestation	1.75
Smoking during pregnancy	0.5

Table A3. Comparative analysis between pregnancies with and without cardiac medication

	All pregnancies	Without cardiac medication	With cardiac medication	*P*-value
	N = 491	*N = 461*	*N = 30*	
mWHO class, n (%):				**<.001**
I	227 (46.2)	218 (47.3)	9 (30.0)	
II	234 (47.7)	226 (49.0)	8 (26.7)	
III	30 (6.11)	17 (3.69)	13 (43.3)	
ESC complexity classification, n (%):				**<.001**
I (mild)	278 (56.6)	269 (58.4)	9 (30.0)	
II (moderate)	176 (35.8)	165 (35.8)	11 (36.7)	
III (severe)	37 (7.54)	27 (5.86)	10 (33.3)	
Cyanotic CHD, n (%)	132 (26.9)	116 (25.2)	16 (53.3)	**.002**
Cardiac events during pregnancy, n (%)	18 (3.67)	6 (1.30)	12 (40.0)	**<.001**
Neonatal events during pregnancy, n (%)	136 (27.7)	115 (24.9)	21 (70.0)	**<.001**

CHD, congenital heart disease; ESC, European Society of Cardiology; mWHO, Modified World Health Organization.

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