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Maternal Outcomes Among Pregnant Women With Congenital Heart Disease–Associated Pulmonary Hypertension

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BACKGROUND: Studies focused on pregnant women with congenital heart disease (CHD)–associated pulmonary hypertension (PH) are scarce and limited by small sample sizes and single-center design. This study sought to describe the pregnancy outcomes in women with CHD with and without PH.

METHODS: Outcomes for pregnant women with CHD were evaluated retrospectively from 1993 to 2016 and prospectively from 2017 to 2019 from 7 tertiary hospitals. PH was diagnosed on the basis of echocardiogram or catheterization. The incidence of maternal death, cardiac complications, and obstetric and offspring complications was compared for women with CHD and no PH, mild, and moderate-to-severe PH.

RESULTS: A total of 2220 pregnant women with CHD had completed pregnancies. PH associated with CHD was identified in 729 women, including 398 with mild PH (right ventricle to right atrium gradient 30–50 mm Hg) and 331 with moderate-to-severe PH (right ventricle to right atrium gradient >50 mm Hg). Maternal mortality occurred in 1 (0.1%), 0, and 19 (5.7%) women with CHD and no, mild, or moderate-to-severe PH, respectively. Of the 729 patients with PH, 619 (85%) had CHD-associated pulmonary arterial hypertension, and 110 (15%) had other forms of PH. Overall, patients with mild PH had better maternal outcomes than those with moderate-to-severe PH, including the incidence of maternal mortality or heart failure (7.8% versus 39.6%; $P<0.001$), other cardiac complications (9.0% versus 32.3%; $P<0.001$), and obstetric complications (5.3% versus 15.7%; $P<0.001$). Brain natriuretic peptide >100 ng/L (odds ratio, 1.9 [95% CI, 1.0–3.4], $P=0.04$) and New York Heart Association class III to IV (odds ratio, 2.9 [95% CI, 1.6–5.3], $P<0.001$) were independently associated with adverse maternal cardiac events in pregnancy with PH, whereas follow-up with a multidisciplinary team (odds ratio, 0.4 [95% CI, 0.2–0.6], $P<0.001$) and strict antenatal supervision (odds ratio, 0.5 [95% CI, 0.3–0.7], $P=0.001$) were protective.

CONCLUSIONS: Women with CHD-associated mild PH appear to have better outcomes compared with women with CHD-associated moderate-to-severe PH, and with event rates similar for most outcomes with women with CHD and no PH. Multimodality risk assessment, including PH severity, brain natriuretic peptide level, and New York Heart Association class, may be useful in risk stratification in pregnancy with PH. Follow-up with a multidisciplinary team and strict antenatal supervision during pregnancy may also help to mitigate the risk of adverse maternal cardiac events.

Key Words: brain natriuretic peptide ■ congenital heart disease ■ multimodality risk assessment ■ pregnancy ■ pulmonary hypertension ■ gender

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Clinical Perspective

What Is New?

- This is the first nationwide, congenital heart disease (CHD)–oriented study specifically describing the maternal pregnancy outcomes in women with CHD-associated pulmonary hypertension (PH) in China.
- The number of women with CHD-associated PH and pregnancy has increased significantly.
- For women with CHD-associated mild PH, adverse events during pregnancy are lower compared with CHD-associated moderate-to-severe PH.

What Are the Clinical Implications?

- Pregnancy outcomes in women with CHD-associated PH differ by PH severity, with worse outcomes seen in women with moderate-to-severe PH, higher brain natriuretic peptide levels, and lower New York Heart Association functional class.
- Multidisciplinary follow-up and strict antenatal supervision associate with lower rates of maternal cardiac complications.
- Currently, all forms and severity of PH have been classified as Modified World Health Organization Classification of Maternal Cardiovascular Risk class IV, where pregnancy is considered contraindicated because of high maternal mortality. The outcomes in the current study suggest that there is variability in this risk, with a subset of patients with PH associated with CHD potentially having a lower risk than previously reported.

Nonstandard Abbreviations and Acronyms

ANC	antenatal care
BNP	brain natriuretic peptide
CHD	congenital heart disease
CHD-PAH	pulmonary arterial hypertension associated with congenital heart disease
HF	heart failure
IQR	interquartile range
LVEF	left ventricular ejection fraction
MDT	multidisciplinary team
mWHO	Modified World Health Organization Classification of Maternal Cardiovascular Risk
NYHA	New York Heart Association
PAH	pulmonary arterial hypertension
PH	pulmonary hypertension
RV-RA	right ventricle to right atrium

Pulmonary hypertension (PH) is known to complicate pregnancy and has historically been associated with unacceptably high maternal mortality (around 25%–56%) because of clinical decompensation secondary to intolerance of the hemodynamic stresses of pregnancy, labor, and delivery.[1–3] Patients with PH of any cause have therefore been classified at the highest risk level in the Modified World Health Organization Classification of Maternal Cardiovascular Risk (mWHO).[1] At this risk level, pregnancy is considered to be contraindicated, and if pregnancy occurs, consensus statements and guidelines recommend that termination be discussed.[1,4] Despite these risks, the incidence of pregnancy in women with pulmonary arterial hypertension (PAH) is increasing.[5] Accordingly, there is an unmet need for identifying and providing optimal care for this subset of patients.

Emerging data have also identified notable differences in maternal outcomes when stratifying pregnant women with PH on the basis of disease subcategory and severity.[3,6–8] Congenital heart disease (CHD)–associated PAH is the most common pathogenesis, accounting for ~65% of PAH during pregnancy.[9] There is some evidence that rates of adverse cardiac events and mortality may be lower relative to other forms of PAH.[10,11] For example, in the Registry of Pregnancy and Cardiac Disease, survival in pregnant women with CHD-associated PAH was 96% versus 57% in those with idiopathic PAH.[3]

There is also some suggestion that patients with less severe PH may have more favorable outcomes versus those with more severe PH.[6,9–12] However, studies of PH severity are limited by small sample sizes. The medical community has therefore highlighted the importance of better identifying individuals in whom pregnancy counseling may be more nuanced, versus completely contraindicated.[9,13] We therefore hypothesized that pregnancy outcomes in women with CHD-associated PH would differ by PH severity.

METHODS

Study Design and Participant Population

This is a retrospective multicenter observational study focused on pregnant women diagnosed with CHD-associated PH at 7 tertiary hospitals in China from April 1993 to December 2019 (Figure S1). The registry was initiated by Shanghai Children's Medical Center, Shanghai Renji Hospital, and Beijing Anzhen Hospital in March 2017. Cases were collected retrospectively from 1993 to 2016 and prospectively from 2017 to 2019. The study was approved by the Shanghai Children's Medical Center institutional review board and by the institutional review boards of other participating centers. All participants enrolled after 2017 gave written informed consent, and informed consent was waived for those enrolled before 2017.

Pregnant women with CHD with and without PH presenting to our hospitals were enrolled. Exclusion criteria (Figure 1) were (1) patients who had incomplete medical records; (2) patients who had miscarriages (fetal death at <24 weeks of

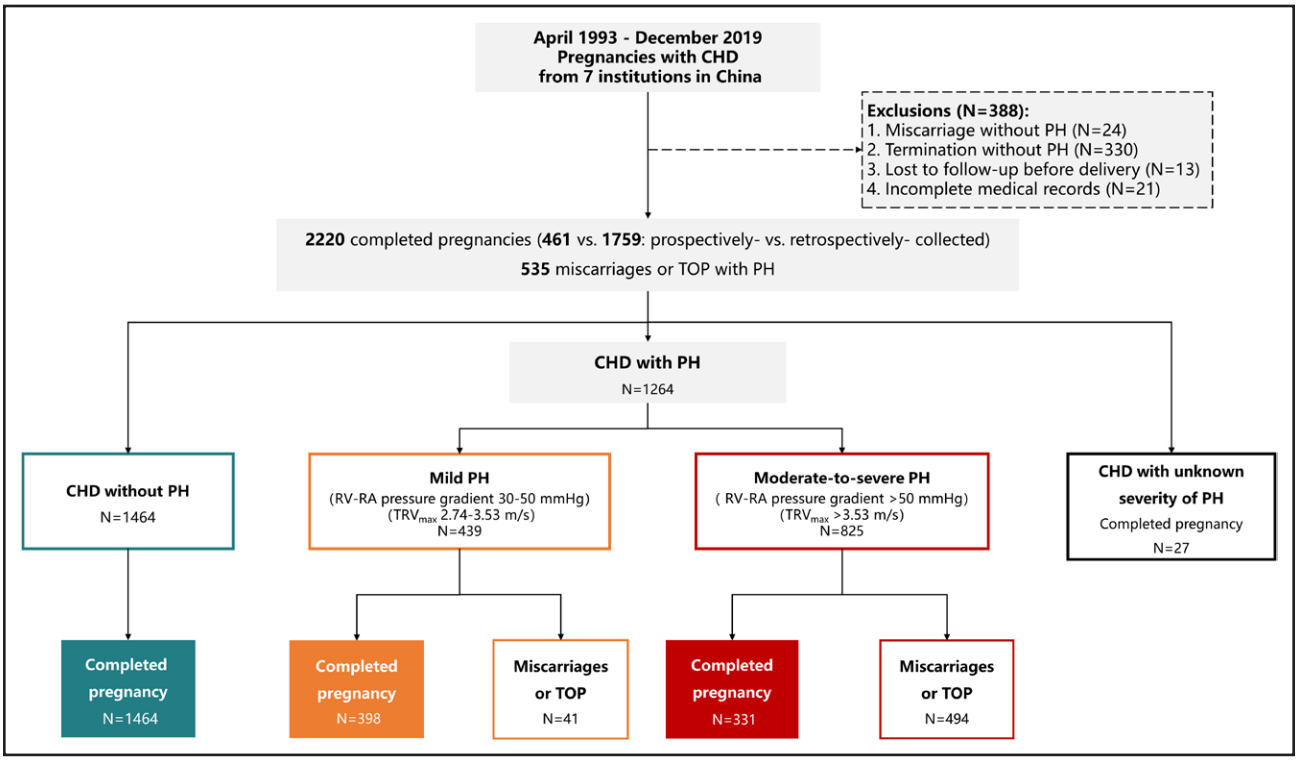

Figure 1. Flow chart of inclusion.
A total of 461 cases were prospectively collected (2017–2019), whereas 1759 were retrospectively collected (1993–2016). In total, 535 women with CHD-associated PH had uncompleted pregnancies including 41 miscarriages at a median gestational week of 12 (IQR, 8–19), and 494 TOP at a median gestational week of 13 (IQR, 9–19). Miscarriages were observed in 7 women with mild PH and 34 women with moderate-to-severe PH, whereas TOP was performed in 34 women with mild PH and 460 women with moderate-to-severe PH. CHD indicates congenital heart disease; PH, pulmonary hypertension; RV-RA, right ventricle to right atrium; TOP, termination of pregnancy; and TRV_{max}, peak tricuspid regurgitation velocity.

gestation) or termination of pregnancy that was not because of PH; and (3) patients who were lost to follow-up before delivery or within 6 weeks postpartum. We used the cutoff time of 6 weeks postpartum because this is a critical phase when maternal and newborn deaths often occur.[14]

Data Access and Collection

The data supporting the study findings are available from the primary corresponding author (H.W.C.) on reasonable request. The baseline visit was the first antenatal care (ANC) visit to 1 of our 7 hospitals. Data collected included patient baseline characteristics (demographics, CHD diagnosis, New York Heart Association [NYHA] functional class, history of arrhythmias), blood tests (brain natriuretic peptide [BNP] level), and findings from the echocardiography (left ventricular ejection fraction [LVEF; for systemic right ventricles, ejection fraction was visually estimated[15]], severity of valvular regurgitation, and estimates of right ventricle to right atrium [RV-RA] pressure gradient) and electrocardiography, and right heart catheterization if available. Of note, BNP was routinely tested in a structured way after 2006 using the Triage B-Type Natriuretic Peptide test (Biosite Inc, San Diego, CA).[16]

PH Diagnosis and Definitions

PH was defined as mean pulmonary arterial pressure ≥20 mm Hg on catheterization or RV-RA pressure gradient ≥30 mm Hg at rest, on the basis of tricuspid regurgitation jet velocity ≥2.74 m/s by echocardiography.[3,17] Patients with PH were further divided into mild PH (mean pulmonary arterial pressure by catheterization 20–40 mm Hg, or echocardiographically estimated RV-RA pressure gradient 30–50 mm Hg at rest [peak tricuspid regurgitation velocity 2.74-3.53 m/s]) and moderate-to-severe PH (mean pulmonary arterial pressure >40 mm Hg by catheterization or echocardiographically estimated RV-RA pressure gradient >50 mm Hg at rest [peak tricuspid regurgitation velocity >3.53 m/s]).[3,17,18] Of note, if there was presence of right ventricular outflow tract obstruction or pulmonary stenosis, the estimation of PH was adjusted as the result of RV-RA pressure gradient minus the right ventricular outflow tract obstruction.[19]

According to the updated classification of PH,[17] CHD-associated PH in this series was subcategorized into CHD-PAH ([group 1], including PAH related to the systemic-to-pulmonary shunt, Eisenmenger syndrome, repaired CHD, and small cardiac defects) and CHD–other PH (including PH related to left heart disease [group 2], pulmonary arterial obstructions [group 4], and complex CHDs [group 5]). Delayed diagnosis of PH was defined as PH diagnosed during pregnancy. Late presentation (also referred to as delayed first ANC visit) was defined as the first prenatal visit to one of the study-associated hospitals that was after the 20th gestational week irrespective of whether they had previously seen doctors in other hospitals (eg, local hospitals). The multidisciplinary team (MDT) included adult cardiologists (including PH experts), congenital heart specialists, obstetricians, neonatologists, and anesthetists who provided a network of tertiary care. Strict antenatal supervision was defined according to

the American College of Obstetricians and Gynecologists guidelines[20] as ≥1 cardiology evaluation during follow-up in patients with mWHO class I, ≥3 evaluations in patients with mWHO class II and II-III, ≥5 evaluations in patients with mWHO class III, and ≥10 evaluations in patients with mWHO class IV. The BNP level was divided into 3 categories (low <35 ng/L, medium 35–100 ng/L, and high >100 ng/L) and was defined to be elevated when it was >35 ng/L.[21] Women with Eisenmenger syndrome were cyanotic patients who had large nonrestrictive systemic-to-pulmonary shunts with pulmonary vascular resistance at systemic levels and shunt reversal (right-to-left).[1] CHD was classified into 4 subcategories (shunt lesions, left heart abnormality, right heart abnormality, and other CHDs; Figure 2). This was done because the well-established European Society of Cardiology[22] (mild, moderate, severe CHD) and anatomic-physiological classifications[23] include PH as part of the classification system, which would have complicated the planned analyses.

Outcomes

Outcome events were analyzed individually and grouped as (1) maternal death or heart failure (HF), (2) other cardiac events, (3) obstetric events, and (4) offspring events. Other cardiac events (diagnosed by expert cardiologists) included clinically significant episodes of arrhythmia requiring treatment, endocarditis, cardiac surgery or interventional treatment during pregnancy, decline of ≥2 NYHA functional classes during pregnancy, thromboembolic event, and myocardial infarction. NYHA deterioration during pregnancy was comprehensively evaluated by experienced cardiologists on the basis of close antenatal supervision. Obstetric events included pregnancy-induced hypertension (new-onset hypertension: systolic blood pressure >140 mm Hg or diastolic >90 mm Hg without proteinuria after 20 weeks of gestation), preeclampsia (a combination of pregnancy-induced hypertension and >0.3 g protein in 24-hour urine sample), eclampsia (preeclampsia with grand mal seizures), hemolysis elevated liver enzymes low platelets syndrome, postpartum hemorrhage (vaginal delivery >500 mL and cesarean section >1000 mL until 6 weeks postpartum), and preterm delivery (<37 weeks of gestation). Preterm delivery was further classified into extremely preterm (<28 weeks), very preterm (28–32 weeks), and moderate or late preterm (32–37 weeks). Offspring events included (1) fetal mortality (demise from in utero [>20 weeks of gestation] to the first year postpartum), including both spontaneous miscarriage and termination of pregnancy; (2) low birth weight (<2500 g), including very low birth weight (<1500 g) and extremely low birth weight (<1000 g); and (3) fetal CHD.

	No PH	Mild PH	Moderate-to-severe PH
CHD Diagnosis			
Shunt lesion	**906 (61.9%)**	**276 (69.3%)**	**241 (72.8%)**
ASD	402 (27.5%)	171 (43.0%)	118 (35.6%)
VSD	366 (25.0%)	86 (21.6%)	103 (31.1%)
PDA	133 (9.1%)	16 (4.0%)	19 (5.7%)
AVSD(PAVSD or CAVSD)	5 (0.3%)	3 (0.8%)	1 (0.3%)
Right heart abnormality	**242 (16.5%)**	**58 (14.6%)**	**29 (8.8%)**
TOF	127 (8.7%)	33 (8.3%)	16 (4.8%)
Ebstein's anomaly	24 (1.6%)	16 (4.0%)	0 (0.0%)
PS(PAS)/PI	69 (4.7%)	2 (0.5%)	8 (2.4%)
DORV	7 (0.5%)	1 (0.3%)	5 (1.5%)
TI	7 (0.5%)	4 (1.0%)	0 (0.0%)
DCRV	6 (0.4%)	1 (0.3%)	0 (0.0%)
Tricuspid valve lesion	0 (0.0%)	1 (0.3%)	0 (0.0%)
PA	2 (0.1%)	0 (0.0%)	0 (0.0%)
Left heart abnormality	**231 (15.8%)**	**40 (10.1%)**	**34 (10.3%)**
AS/AI	90 (6.1%)	18 (4.5%)	15 (4.5%)
MS/MI	111 (7.6%)	15 (3.8%)	14 (4.2%)
Mitral valve lesion	0 (0.0%)	2 (0.5%)	4 (1.2%)
CoA	21 (1.4%)	4 (1.0%)	1 (0.3%)
Aortic valve lesion	0 (0.0%)	1 (0.3%)	0 (0.0%)
Marfan Syndrome	9 (0.6%)	0 (0.0%)	0 (0.0%)
Other CHDs	**85 (5.8%)**	**24 (6.0%)**	**27 (8.2%)**
Unidentified CHD	29 (2.0%)	9 (2.3%)	7 (2.1%)
APVC (total or partial)	8 (0.5%)	4 (1.0%)	6 (1.8%)
Functional Single Ventricle	8 (0.5%)	1 (0.3%)	6 (1.8%)
L-TGA	14 (1.0%)	2 (0.5%)	4 (1.2%)
TGA	7 (0.5%)	4 (1.0%)	2 (0.6%)
Mechanical Valve Replacement (detailed valve is unknown)	15 (1.0%)	3 (0.8%)	0 (0.0%)
Truncus	2 (0.1%)	0 (0.0%)	2 (0.6%)
ALCAPA	2 (0.1%)	1 (0.3%)	0 (0.0%)
PH Subcategory			
CHD-PAH	/	346 (86.9%)	273 (82.5%)
CHD-oPH	/	52 (13.1%)	58 (17.5%)

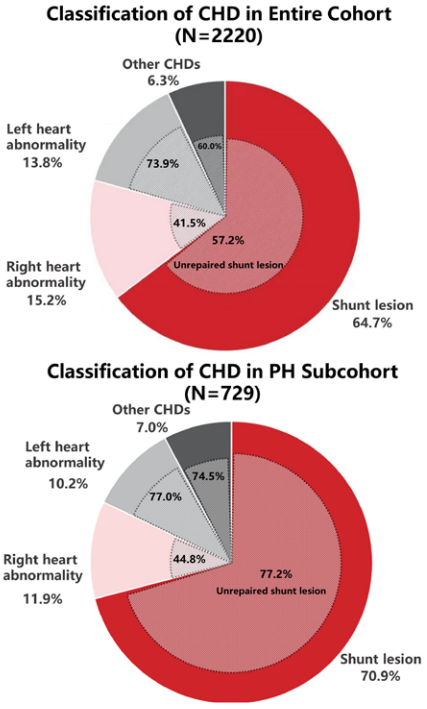

Figure 2. Classification of CHD diagnosis.

Left, The 4 subcategories of CHD as well as the detailed diagnosis in each subcategory in patients with CHD and no PH, CHD-associated mild PH, and CHD-associated moderate-to-severe PH. **Right**, Pie charts, percentage of unrepaired CHD in each subcategory in the entire cohort and CHD-associated PH subcohort. Tricuspid/mitral/aortic valve lesion indicated that valvar stenosis or regurgitation cannot be identified. AI indicates aortic valve insufficiency; ALCAPA, anomalous left coronary artery from the pulmonary artery; APVC, anomalous pulmonary venous connection; AS, aortic valve stenosis; ASD, atrial septal defect; AVSD, atrioventricular septal defect; CAVSD, complete atrioventricular septal defect; CHD, congenital heart disease; CHD-oPH, CHD-other PH; CHD-PAH, pulmonary arterial hypertension associated with congenital heart disease; CoA, coarctation of aorta; DCRV, double chambered right ventricular; DORV, double outlet right ventricle; L-TGA, L-looped transposition of the great arteries; MI, mitral valve insufficiency; MS, mitral valve stenosis; PA, pulmonary atresia; PAS, pulmonary artery stenosis; PAVSD, partial atrioventricular septal defect; PDA, patent ductus arteriosus; PH, pulmonary hypertension; PI, pulmonary valve insufficiency; PS, pulmonary valvar stenosis; TGA, transposition of the great arteries; TI, tricuspid valve insufficiency; TOF, tetralogy of Fallot; and VSD, ventricular septal defect.

Statistical Analysis

Categorical data were presented as frequencies (numbers) and percentages, whereas continuous data were presented as mean±SD or median (interquartile range [IQR]) values. Comparisons between 2 groups were performed using the Student *t* test or Wilcoxon rank test for continuous variables and the chi-square or Fisher exact test for categorical variables. Comparisons among multiple groups were performed using the ANOVA or Kruskal-Wallis test for continuous variables and the chi-square or Fisher exact test for categorical variables. Normality of continuous data was checked with Kolmogorov-Smirnov tests. To identify the risk factors for cardiac outcomes, univariable and multivariable analyses were performed through logistic regression. The candidate variables included demographics, general and lesion-specific cardiac characteristics, and laboratory examinations. Univariable predictors of adverse cardiac events with *P* values of <0.1 were selected and entered in the multivariable logistic regression model with a level of significance at 0.05. Odds ratios and 95% CIs were reported in a forest plot. Subgroup analyses were performed by comparing the incidence of maternal cardiac events in each subgroup of pregnancies with mild PH. We applied propensity score matching analyses between the no-PH group and mild-PH group. Each patient's propensity score was estimated by a multivariable logistic regression model with covariates. Patients with no PH were matched in a 1:1 ratio with no replacement to patients with mild PH using the nearest-neighbor algorithm. Two-tailed *P* values <0.05 were considered statistically significant. All statistical analyses were performed with R Project Software (version 3.6.3, R Foundation).

RESULTS

Population

A total of 2220 pregnancies in women with CHD were included in the main analyses. Mean maternal age was ~28 years, and most (60%) were nulliparous. No women had multiple pregnancies during the study. The diagnosis of PH (probable PH) was based on echocardiogram in most, although catheterization was used for diagnosis when performed (N=58; correlation versus echocardiogram r=0.83, P<0.001, Figure S2). Patients were further divided into mild PH (N=729, median RV-RA pressure gradient 37 mm Hg [IQR, 33.0–43.0]) and moderate-to-severe PH [N=331, median RV-RA pressure gradient 72 mm Hg (IQR, 56.0–96.5]) (Figure 1). The severity of PH could not be identified in 27 patients because of missing data about the RV-RA pressure gradient; thus, these patients were excluded from the main analyses.

Detailed patient demographics are shown in Table 1. Most women with PH had a normal LVEF (96.7%), defined as an ejection fraction >50%, regardless of the severity of PH. Women with moderate-to-severe PH had poorer NYHA functional class (30.2% versus 3.3%, P<0.001) and higher BNP level (>100 ng/L; 24.8% versus 13.3%, P<0.001) than those in the mild PH group.

PH Pathogenesis and Timing of Diagnosis

Of the 729 women with CHD-associated PH, 619 had CHD-PAH, and 110 had CHD–other PH. Systemic-to-pulmonary shunt-related PAH was most common (75.4%; 467/619) in the CHD-PAH group, whereas left heart disease–related PH was the most common (50.9%; 56/110) in the CHD–other PH group. Delayed diagnosis of PH, defined as a PH diagnosis made during pregnancy, occurred in 228 women (31.3%; 228/729), among whom 149 (20.4%) were diagnosed after their 20th gestational week. First visit to a specialty hospital after 20 weeks (delayed first ANC visit) occurred in 68.6% in the PH subcohort. Underlying CHD pathogenesis is shown in Figure 2.

Management

The median duration of follow-up during pregnancy from first ANC visit to delivery was 98 (IQR, 70–140) days, and the median duration of postpartum follow-up was 53 (IQR, 48–59) days. Around two-thirds of the 729 women with PH were followed with strict antenatal supervision, meeting the minimum number of visits recommended in American College of Obstetricians and Gynecologists guidelines (Table 2), and 537 (74%) had at least 2 echocardiographic examinations. PH severity was unchanged for most women (89%) between the first and last ANC visits during pregnancy, whereas 11% changed PH severity category (Figure S3).

Oxygen supplementation and diuretics were provided to 462 (63.4%) and 347 (47.6%) of patients with PH, respectively, during pregnancy, and all women with PH were counseled to avoid excessive physical activity. PH targeted therapy was received by 128 women (17.6%, 128/729), including 29 (7%) women with mild PH and 99 (30%) women with moderate-to-severe PH (Table 2). Intensive care unit admission was required in 6.5% (26/398) of women with mild PH and 68.3% (226/331) of women with moderate-to-severe PH, and the median length of hospital stay was 7 (IQR, 5–10) and 10 (IQR, 6–13) days in the mild and moderate-to-severe PH subgroups, respectively.

Most women in all 3 groups were delivered by cesarean section using regional anesthesia, with cesarean section used in 83%, 89%, and 92% of women with no, mild, and moderate-to-severe PH (P<0.05 for comparison between no PH and mild PH; Table 2). Preterm and very preterm deliveries were more common in women with moderate-to-severe PH (Table 2).

Maternal Outcomes

Maternal mortality occurred in 1 (0.1%), 0, and 19 (5.7%) women with CHD and no, mild, or moderate-to-severe PH, respectively (P<0.001 for

Table 1. Baseline Characteristics

	No PH (N=1464)	Mild PH (N=398)	Moderate-to-Severe PH (N=331)	*P* value*	*P* value†
Age,‡ y, mean±SD	28.3±4.4	28.2±4.5	27.6±4.6	0.72	0.075
Hypertension or diabetes, n (%)	96 (6.6%)	21 (5.3%)	36 (10.9%)	0.42	0.006
Previous arrhythmia, n (%)	200 (13.7%)	72 (18.1%)	32 (9.7%)	0.001	<0.001
Unrepaired CHD, n (%)	712 (48.6%)	259 (65.1%)	274 (82.8%)	<0.001	<0.001
Cyanotic CHD, n (%)	189 (12.9%)	54 (13.6%)	32 (9.7%)	0.19	0.064
RV-RA pressure gradient,§ mm Hg, median (IQR)	24.0 (22.0–27.0)	37.0 (33.0–43.0)	72.0 (56.0–96.5)	<0.001	<0.001
NYHA, n (%)				0.014	<0.001
I–II	1443 (98.6%)	383 (96.2%)	204 (61.6%)	…	…
III–IV	19 (1.3%)	13 (3.3%)	100 (30.2%)	…	…
LVEF, n (%)				0.067	0.81
0%–50%	14 (1.0%)	9 (2.3%)	9 (2.7%)	…	…
>50%	1446 (98.8%)	387 (97.2%)	318 (96.1%)	…	…
BNP‖, n (%), ng/L				…	…
<35	928 (63.4%)	178 (44.7%)	132 (39.9%)	<0.001	0.40
35–100	375 (25.6%)	164 (41.2%)	102 (30.8%)	<0.001	0.013
>100	158 (10.8%)	53 (13.3%)	82 (24.8%)	0.15	<0.001
Nulliparity, n (%)	891 (60.9%)	238 (59.8%)	203 (61.3%)	0.73	0.70
Multiple gestation, n (%)	29 (2.0%)	4 (1.0%)	5 (1.5%)	0.28	0.74
Assisted reproduction, n (%)	41 (2.8%)	11 (2.8%)	5 (1.5%)	1.000	0.31
Abnormal pregnancy history,¶ n (%)	157 (10.7%)	31 (7.8%)	44 (13.3%)	0.091	0.020
Follow-up time after delivery,§ d, median (IQR)	53 (47–59)	53.5 (47–60)	54 (49–59)	0.31	0.80
Follow-up time after the first ANC visit,§ d, median (IQR)	160.5 (128.0–213.3)	162.5 (124.0–217.0)	136.0 (104.0–189.0)	0.69	<0.001

ANC indicates antenatal care; BNP, brain natriuretic peptide; CHD, congenital heart disease; IQR, interquartile range; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PH, pulmonary hypertension; and RV-RA, right ventricle to right atrium.

**P* value between patients in no PH group and mild PH group.

†*P* value between patients in mild PH group and moderate-to-severe PH group.

‡Comparisons of maternal age between 2 groups (no PH versus mild PH; mild PH versus moderate-to-severe PH) were performed using the Student *t*-test.

§Comparisons of RV-RA pressure gradient, follow-up time after delivery, and follow-up time after the first ANC visit between 2 groups (no PH versus mild PH; mild PH versus moderate-to-severe PH) were performed using the Wilcoxon rank test.

‖BNP data obtained at a median of 23 (IQR, 18–27) weeks of gestation for patients recruited after year 2000 and were available in 2173 of 2220 (overall patient population) and in 711 of the 729 patients with PH.

¶Abnormal pregnancy history, included the history of miscarriage, ectopic pregnancy, fetal abnormalities, or intrauterine death.

moderate-to-severe versus mild and versus no PH; Table 2). Three of 19 deaths (16%) in PH women occurred during the delivery, whereas the remainder occurred during the postpartum period (Table S1, detailed causes of death). Among the 535 women with uncompleted pregnancies (miscarriage or termination of pregnancy), maternal mortality occurred in 16 of 494 women in the moderate-to-severe PH group (3.2%), versus no women in the no PH and mild PH groups (Figure S4, outcomes for completed and uncompleted pregnancies combined).

HF, arrhythmia requiring treatment, and decline of ≥2 NYHA functional classes also occurred more often in women with moderate-to-severe PH (Table 2), whereas there were no significant differences in these individual end points for the women with CHD and no PH versus mild PH. When analyzed by event category (Figure 3), women with moderate-to-severe PH had worse outcomes for death/HF, other cardiac events, offspring events, and obstetric events compared with the mild PH group. In contrast, women with mild PH had a significantly higher event rate versus patients with CHD and no PH only in the combined other cardiac events category.

Factors associated with maternal cardiac complications in the cohort overall and in the PH associated with CHD subcohort are shown in Figure 4. In the multivariable analysis including all 2220 patients (Figure 4B), maternal cardiac events were significantly associated with moderate-to-severe PH, increased BNP level (>35 ng/L), NYHA class III to IV, unrepaired CHD, LVEF <50%, and delayed first ANC visit, but not with mild PH (*P*=0.70). Follow-up with the MDT and with strict antenatal supervision were both protective. Within the PH subcohort (N=729), increased BNP >100 ng/L and NYHA III to IV remained risk predictors for maternal cardiac events, but BNP levels of 35 to 100 ng/L and LVEF <50% were not (Figure 4D).

Table 2. Clinical Outcomes and Management in Pregnancies With No PH, Mild PH, and Moderate-to-Severe PH

	No PH (N=1464)	Mild PH (N=398)	Moderate-to-severe PH (N=331)	*P* value*	*P* value†	*P* value‡
Clinical outcomes						
Maternal cardiac events, n (%)						
Death	1 (0.1%)	0 (0.0%)	19 (5.7%)	1.00	<0.001	<0.001
Heart failure	94 (6.4%)	31 (7.8%)	128 (38.7%)	0.37	<0.001	<0.001
Arrhythmia requiring treatment	36 (2.5%)	16 (4.0%)	20 (6.0%)	0.12	0.23	0.002
Endocarditis	2 (0.1%)	1 (0.3%)	3 (0.9%)	0.51	0.34	0.046
Cardiac surgery during the prenatal period	16 (1.1%)	8 (2.0%)	4 (1.2%)	0.21	0.56	0.78
Decline of ≥2 NYHA functional class during the antepartum period	25 (1.7%)	12 (3.0%)	85 (25.7%)	0.11	<0.001	<0.001
Thromboembolic event	5 (0.3%)	2 (0.5%)	1 (0.3%)	0.63	1.00	1.00
Cerebrovascular event	1 (0.1%)	0 (0.0%)	0 (0.0%)	1.00	1.00	1.00
Myocardial infarction	6 (0.4%)	2 (0.5%)	2 (0.6%)	0.65	1.00	0.63
Obstetric events, n (%)						
Preterm delivery (<37 wk)	204 (13.9%)	67 (16.8%)	144 (43.5%)	0.15	<0.001	<0.001
Very preterm (28–32 wk)	16 (1.1%)	9 (2.3%)	44 (13.3%)	0.085	<0.001	<0.001
Extremely preterm (<28 wk)	2 (0.1%)	1 (0.3%)	1 (0.3%)	0.51	1.00	0.46
Postpartum hemorrhage	73 (5.0%)	9 (2.3%)	37 (11.2%)	0.019	<0.001	<0.001
Pregnancy induced hypertension	49 (3.3%)	14 (3.5%)	12 (3.6%)	0.88	1.00	0.74
Preeclampsia	44 (3.0%)	8 (2.0%)	23 (6.9%)	0.39	0.001	0.002
HELLP	0 (0.0%)	0 (0.0%)	5 (1.5%)	1.00	0.019	<0.001
Offspring events, n (%)						
Offspring death	7 (0.5%)	1 (0.3%)	4 (1.2%)	1.00	0.18	0.13
Low birth weight	167 (11.4%)	64 (16.1%)	145 (43.8%)	0.016	<0.001	<0.001
Very low birth weight	13 (0.9%)	8 (2.0%)	36 (10.9%)	0.10	<0.001	<0.001
Extremely low birth weight	8 (0.5%)	2 (0.5%)	8 (2.4%)	1.00	0.049	0.004
Offspring CHD	40 (2.7%)	10 (2.5%)	13 (3.9%)	1.00	0.30	0.28
Management						
Antenatal management, n (%)						
Late presentation (>20 wk gestation)	969 (66.2%)	250 (62.8%)	250 (75.5%)	0.21	<0.001	0.001
Strict antenatal supervision	1320 (90.2%)	275 (69.1%)	196 (59.2%)	<0.001	0.006	<0.001
Total times of antenatal visit,§ mean±SD	8.0±3.3	9.2±3.2	7.6±4.6	<0.001	<0.001	0.091
Total weeks followed from presentation to delivery,‖ median (IQR)	15 (11–21)	15 (10–20)	11 (7–16.6)	0.39	<0.001	<0.001
MDT	1009 (68.9%)	251 (63.1%)	152 (45.9%)	0.030	<0.001	<0.001
Delivery management, n (%)						
Gestational week at delivery,‖ mean±SD	37.8±1.9	37.4±2.1	35.6±3.1	<0.001	<0.001	<0.001
Length of hospital stay,‖ d, median (IQR)	7 (5–9)	7 (5–10)	10 (6–13)	0.18	<0.001	<0.001
Mode of delivery				0.005	0.17	<0.001
Vaginal	246 (16.8%)	44 (11.1%)	26 (7.9%)	…	…	…
Caesarean section	1218 (83.2%)	354 (88.9%)	305 (92.1%)	…	…	…
Anesthesia						
General anesthesia	36 (2.5%)	9 (2.3%)	38 (11.5%)	1.00	<0.001	<0.001
Regional anesthesia	1209 (82.6%)	347 (87.2%)	273 (82.5%)	0.027	0.095	1.00
Without anesthesia	219 (15.0%)	42 (10.6%)	19 (5.7%)	0.028	0.022	<0.001

(*Continued*)

Table 2. Continued

	No PH (N=1464)	Mild PH (N=398)	Moderate-to-severe PH (N=331)	*P* value*	*P* value†	*P* value‡
Drug therapy, n (%)						
Targeted therapy	…	29 (7.3%)	99 (29.9%)	…	<0.001	…
Monotherapy¶	…	26 (6.5%)	68 (20.5%)	…	<0.001	…
Combination therapy#	…	3 (0.8%)	31 (9.4%)	…	<0.001	…
Anticoagulation	11 (0.8%)	20 (5.0%)	25 (7.6%)	<0.001	0.17	<0.001

CHD indicates congenital heart disease; HELLP, hemolysis elevated liver enzymes low platelets syndrome; IQR, interquartile range; MDT, multidisciplinary team; NYHA, New York Heart Association; PDE5-i, phosphodiesterase type 5 inhibitor; and PH, pulmonary hypertension.

*P value between patients in no PH group and mild PH group.

†P value between patients in mild PH group and moderate-to-severe PH group.

‡P value between patients in no PH group and moderate-to-severe PH group.

§Comparisons of total times of antenatal visit between 2 groups (no PH versus mild PH; mild PH versus moderate-to-severe PH; no PH versus moderate-to-severe PH) were performed using the Student *t*-test.

‖Comparisons of total weeks followed from presentation to delivery, gestational week at delivery, and length of hospital stay between 2 groups (no PH versus mild PH; mild PH versus moderate-to-severe PH; no PH versus moderate-to-severe PH) were performed using the Wilcoxon rank test.

¶Monotherapy included PDE5-i (including oral sildenafil or tadalafil), inhaled iloprost, intravenous treprostinil, or intravenous alprostadil.

#Combination therapy included PDE5-i and intravenous treprostinil.

Offspring Adverse Events

The mean gestational week at delivery was 37.8±1.9, 37.4±2.1, and 35.6±2.1 weeks for no PH, mild PH, and moderate-to-severe PH, respectively. The most frequent offspring event was low birth weight (17.2%), and both low birth weight and combined offspring events overall occurred more often in the moderate-to-severe PH group (Table 2 and Figure 3). Offspring mortality occurred in 7 (0.5%), 1 (0.3%), and 4 (1.2%) women with no PH, mild PH, and moderate-to-severe PH (*P*, NS for all comparisons).

Time Trend Analyses

During the study period, the proportion of pregnant women with CHD-associated PH increased from 13.4% for the earliest study years (1993–2004) to 39.0% in the most recent years (2015–2019) (Figure 5A). A greater proportion of women also had poorer functional class (NYHA III–IV), an elevated BNP (>35 ng/L), and moderate-to-severe PH (Table S2) in the most recent years. Shunt lesions (repaired or unrepaired) remained the most common subgroup in women with CHD-associated PH, despite a nearly 10% decrease from 1993 to 2004 to 2015 to 2019 (Figure S5). Repaired CHD increased over time, reaching 23.2% (45/194) for the years 2015 to 2019 (Figure S6).

Adverse maternal outcomes in women with moderate-to-severe PH declined from 75% in 1993 to 2004 to 39.7% in 2015 to 2019, combining events of maternal death, HF, and other cardiac events (Figure 5B). This occurred simultaneously with an increase in termination of pregnancy among women with moderate-to-severe PH (from 29.4% to 68.2%, Figure S6). The event rates for maternal and offspring outcomes were similar in the retrospectively collected (n=1759) and prospectively collected subcohorts (n=461) (Figure S7).

Sensitivity Analyses

Sensitivity analyses were completed to evaluate outcomes after grouping by (1) repaired CHD, (2) unrepaired CHD, and (3) CHD-PAH (ie, excluding patients with other forms of PH). In all 3 cases, the moderate-to-severe PH group had higher rates of adverse events for maternal death or heart failure (combined), other cardiac events, offspring events, and obstetric events, whereas events for the mild PH and no PH groups were similar for most end points (Figure S8 through S10). Outcomes were also generally similar for women with and without 1 or more previous pregnancies (Figure S11 through S13; Table S3, detailed comparisons between women with and without previous pregnancies).

Between-Group Comparison in CHD Women With Mild Versus No PH

Propensity score matching resulted in 2 well-balanced groups consisting of 392 patients with CHD-associated mild PH and 392 with CHD and no PH. There was no significant difference in maternal death/HF (11.0% versus 7.1%; *P*=0.08) or offspring outcomes (20.9% versus 16.8%; *P*=0.17) for the mild versus no PH groups (Table S4). In a separate analysis exploring subgroups within the mild PH group, a higher rate of adverse maternal events was seen in women with a LVEF <50% (4/9, 44%) and NYHA class III/IV symptoms (7/13, 54%), although the small number of patients in these subgroups limits this analysis (Figure S14).

DISCUSSION

This nationwide study, to our knowledge, represents the largest study on pregnancy in women with CHD-associated PH. Herein, the main findings from the

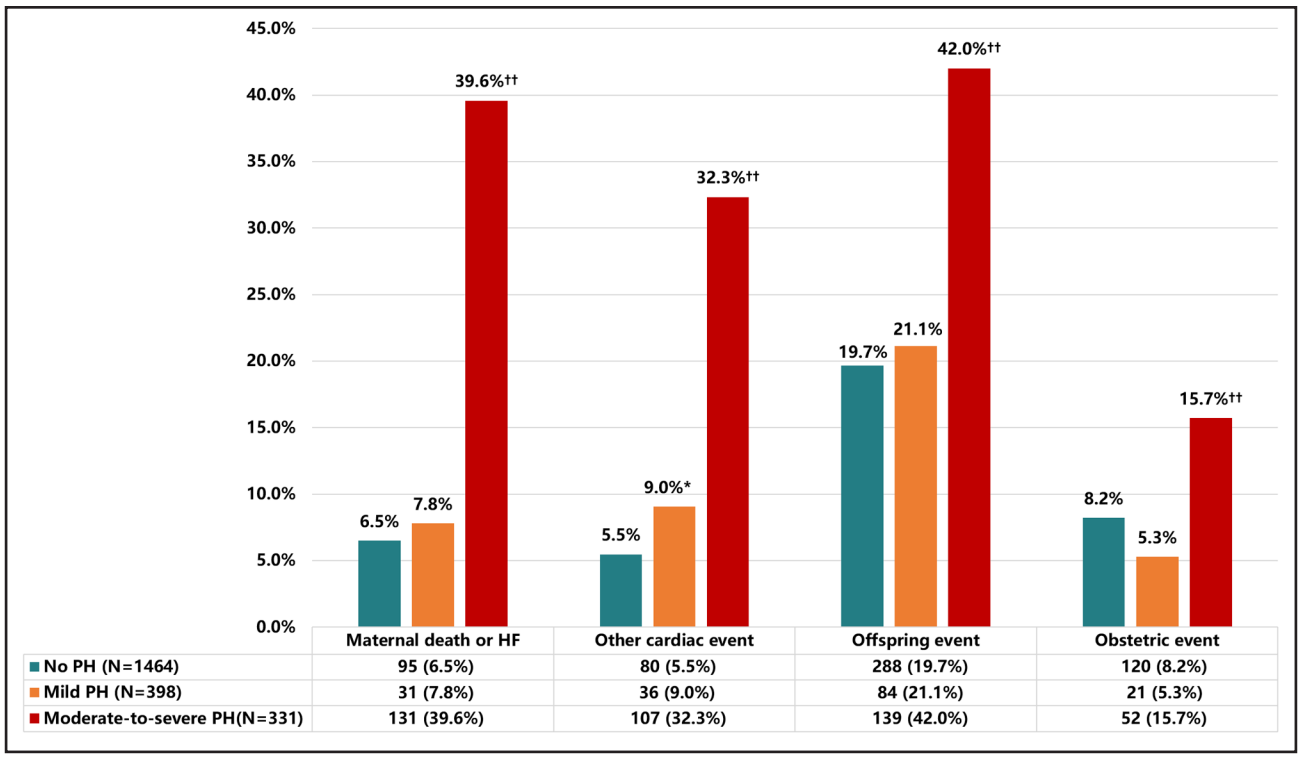

Figure 3. Adverse events in patients with CHD-associated PH and without PH.
For women who completed pregnancy, those with CHD-associated mild PH had similar outcomes compared with those with no PH in terms of maternal and offspring outcomes, except for a higher incidence of other cardiac event. However, there was a significantly higher incidence of maternal and offspring complications in those with moderate-to-severe PH than in mild PH. Other cardiac events included clinically significant episodes of arrhythmia, endocarditis, myocardial infarction, thromboembolic events, decline of ≥2 New York Heart Association functional classes during pregnancy, and cardiac surgery/interventional treatment during pregnancy. *Significant difference ($P<0.05$) between patients with no PH and mild PH. ††Significant difference ($P<0.01$) between patients with mild PH and moderate-to-severe PH. CHD indicates congenital heart disease; HF, heart failure; and PH, pulmonary hypertension.

analysis of 2220 CHD women with completed pregnancies (34% with PH versus 66% without PH) are 3-fold. First, women with mild PH had lower rates of adverse outcomes for maternal death, cardiac events, offspring events, and obstetric events compared with the moderate-to-severe PH subgroup, and had similar outcomes versus CHD and no PH in the propensity score–matched analysis. Second, follow-up with the MDT and with strict antenatal supervision were both associated with lower rates of maternal cardiac complications in patients with CHD-associated PH. Third, taking BNP level and NYHA functional class into consideration may help to further risk-stratify pregnant women with CHD-associated mild or moderate-to-severe PH.

These results suggest that a more individualized approach to pregnancy risk may need to be considered in the future for women with pregnancy and CHD-associated PH. Previous studies have shown declining but still unacceptably high maternal mortality rates for women with pregnancy and PH in general, falling from 56% in 1978 to 1996 to 12% in 2008 to 2018.[9,24] For the CHD-PAH subset, some studies have also suggested an even lower mortality rate (3.6%–6.4%).[3,25] However, overall maternal morbidity and mortality as well as offspring events remained unacceptably high in these studies. In this context, the findings from the present work provide important information suggesting that pregnancy outcomes in women with CHD-associated PH may also differ by PH severity, and that potentially, CHD with mild PH with other favorable findings may not be an absolute contraindication to pregnancy.

Our study overall has also shown a lower maternal mortality (2.6%) in pregnant women with CHD-associated PH than previously reported, although still higher than in healthy pregnant women. We also found that adverse maternal cardiac events declined over time in women with moderate-to-severe PH (Figure 5). The lower mortality rate overall may in part be attributable to the patient population, where the majority of the patients had systemic-to-pulmonary shunt-related PAH (excluding Eisenmenger syndrome) and who, in other studies,[3,6,9,25] have been reported to tolerate pregnancy better related to better right ventricular compensation. However, early assessment by the MDT, including timely first ANC visit, access to tertiary care, follow-up with the MDT, and strict antenatal supervision, may also have contributed to improved outcomes. These interventions are in line with current guidelines for the management of

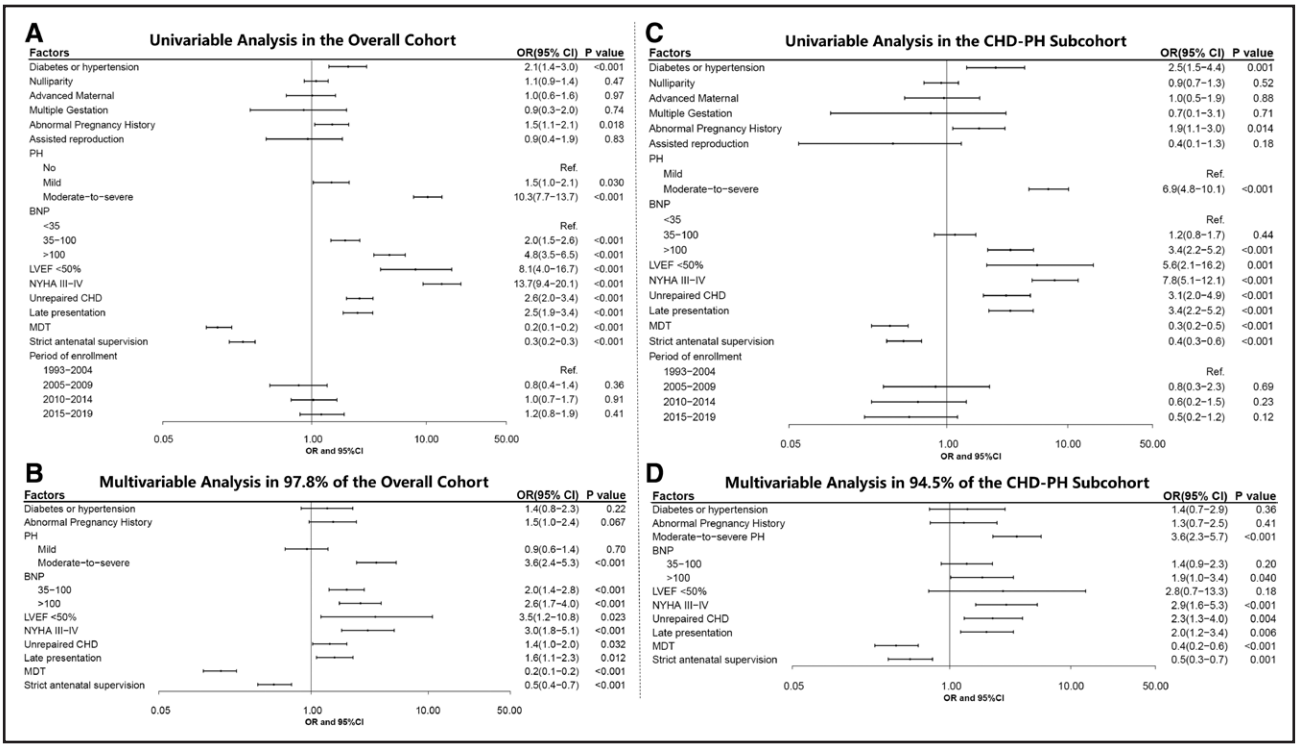

Figure 4. Univariable and multivariable analyses of maternal cardiac events in the entire cohort and CHD-associated PH subcohort.

Univariable and multivariable analyses were performed to explore the risk factors associated with maternal cardiac complications in the overall cohort (**A** and **B**) and in patients with CHD-associated PH (**C** and **D**). Missing data for PH severity, BNP level, LVEF, or NYHA class occurred in 93 patients who were excluded, and thus the analyses were performed in 2127 of 2220 patients (97.8%) overall (**B**), and in 689 of 729 (94.5%) of patients in the PH associated with CHD subcohort (**D**). ORs and 95% CIs were estimated using the logistic regression model. Variables with a *P* value <0.10 identified in the univariable analyses were entered into the multivariable analyses. BNP indicates brain natriuretic peptide; CHD, congenital heart disease; LVEF, left ventricle ejection fraction; MDT, multidisciplinary team; NYHA, New York Heart Association; OR, odds ratio; and PH, pulmonary hypertension.

pregnant patients with increased risk of cardiovascular complications,[1,4] and were more commonly performed in women in the more recent years of the study (Table S2).

Another potential contributor to favorable outcomes may be the liberal use of cesarean section under regional anesthesia (~93%), which potentially avoids maternal decompensation in the late stages of pregnancy. Regional anesthesia was preferred over general anesthesia so as to avoid potential negative effects on cardiac contractility and pulmonary vascular resistance,[26] although there is a lack of strong evidence to support the superiority of cesarean section over vaginal delivery or regional versus general anesthesia, in terms of improving maternal outcomes.[27]

It is important that women with CHD-associated mild PH had significantly lower rates of maternal and offspring complications during pregnancy than those with moderate-to-severe PH (Figure 3). This can likely be attributed to better preserved RV function, resulting in better compensation with the increased cardiac demands seen during pregnancy. In addition, after adjustment for the baseline characteristics, patients with mild PH had similar outcomes versus those having CHD and no PH, with no evidence of significantly increased risk in maternal death/HF or obstetric or fetal complications. PH severity was also unchanged for most women (84.7%) between the first and last ANC visits, with 89.0% and 80.9% for mild and moderate-to-severe PH, respectively (Figure S3).

Recent guidelines for PAH in general (outside of pregnancy) have proposed a comprehensive evaluation and individualized risk stratification in patients with PAH, with both functional class and BNP levels playing a prominent role in this assessment.[4] Correspondingly, our work also suggests that multimodality assessment, including disease severity (mild versus moderate-to-severe PH on the basis of RV-RA pressure gradient), BNP level, and NYHA class, may be useful in assessing risk in pregnancy with CHD-associated PH. BNP is a marker of myocardial stress and is widely used in the routine practice of specialized PH centers because of its association with mortality and correlation with pulmonary hemodynamics.[4,28] Poorer NYHA functional class is also a known predictor of major adverse cardiac events in pregnant women with cardiac disease.[29]

It is interesting that LVEF <50% was not found to be a risk predictor for maternal cardiac events. A reasonable explanation may be that RV size and function are often

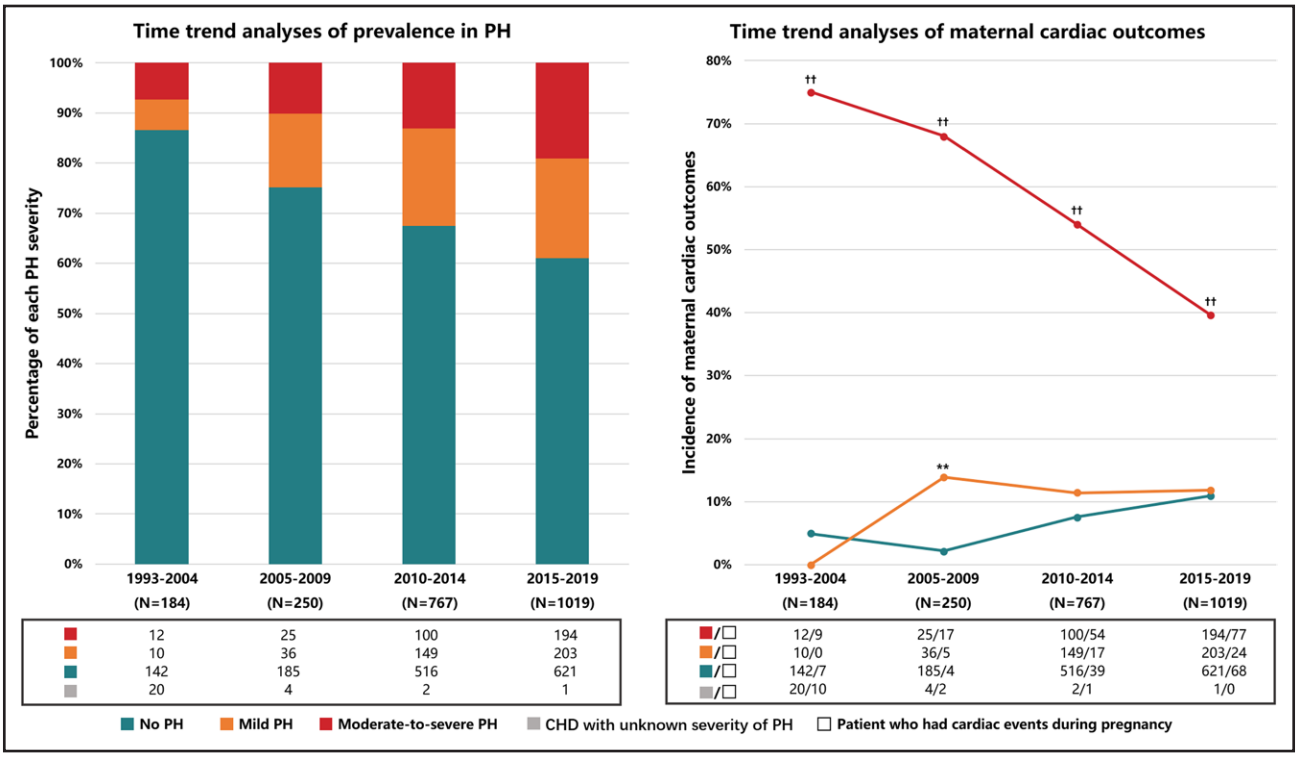

Figure 5. Time trend analyses of PH prevalence and of maternal cardiac outcomes in the overall cohort (n=2220).
Left, Change of case mix in patients with CHD-associated PH of different degrees (no, mild, moderate-to-severe PH) during the study period. **Right**, Incidences of maternal cardiac outcomes in each subgroup in the 4 periods of enrollment (1993–2004, 2005–2009, 2010–2014, and 2015–2019). Maternal cardiac outcomes included maternal death, heart failure, clinically significant (requiring treatment with at least prescription drugs) episodes of arrhythmia, endocarditis, cardiac surgery or interventional treatment during pregnancy, decline of ≥2 New York Heart Association functional classes during pregnancy, thromboembolic event, and myocardial infarction. **Significant difference between patients in the no PH group and mild PH group ($P<0.01$). ††Significant difference between patients in the mild PH group and moderate-to-severe PH group ($P<0.01$). Between-group comparisons in the incidences of the maternal cardiac outcomes were performed using the Fisher exact test. CHD indicates congenital heart disease; and PH, pulmonary hypertension.

better predictors of outcome in CHD with and without PH, whereas LVEF is generally less predictive.[30–32] In future studies, additional echocardiographic measures of cardiac size and function should be considered for inclusion, because measures such as right atrial size, right ventricular size and function, and pericardial effusion also associate significantly with PH outcomes.

Of note, it appears to be counterintuitive that women with moderate-to-severe PH (especially related to unrepaired shunt lesion) increased in prevalence over the years, given better prenatal diagnosis of CHD and also corrective repair afterwards. Possible explanations are as follows. First, there was a lack of access to timely CHD repair in rural or remote areas in a portion of these women in this series, potentially reflecting the socioeconomic disparities between the developed and developing world. Second, with the implementation of regionalization of care for pregnant women in China in the more recent era, a higher proportion of these women may now be referred to specialty hospitals. Third, a change in the case mix over time may suggest true changes in the pathogenesis of CHD in women with moderate-to-severe PH. Last, improved outcomes for more severe forms of CHD may have led to an increase in some subgroups of patients surviving to adulthood.[33]

Limitations

This study has many limitations. First, most patients were diagnosed with PH by echocardiography because of patient or physician preference. This may have led to overdiagnosis or underdiagnosis, particularly for those with pressures near our cutoffs, and it is possible that a subset of patients may have elevated pulmonary pressures primarily caused by increased cardiac output (ie, with normal pulmonary vascular resistance). However, our classification of PH using RV-RA pressure gradient without adding the right atrium pressure is more conservative versus other CHD registries. For example, in the multicenter Registry of Pregnancy and Cardiac Disease, an RVSP ≥30 mm Hg (including estimated right atrium pressure) was used to define PH.[4] Second, although this study was conducted across 7 Chinese hospitals, our sites were mostly high-volume academic medical centers. Thus, the results may not be applicable to hospitals with less extensive resources. Third, patients in this study

were enrolled across a wide timespan (>2 decades), which may have introduced era-related confounding influences such as advancements in diagnostic imaging modality, specialized care, and PH-targeted therapies. Fourth, although the sensitivity analysis in 535 women who had miscarriage or termination related to PH (moderate-to-severe PH: 92.3% [494/535]) showed the results consistent with the primary analysis, there is still the potential that higher-risk patients may have been more likely to terminate at an early/lower-risk time point in pregnancy, potentially resulting in a lower overall mortality risk than would be seen in settings where termination is less common or prohibited. Whether our results can be extrapolated to other PAH subgroups (ie, idiopathic PAH) is also unknown. Last, although most postpartum deaths in pregnant women occur within 1 month of delivery, the effects of pregnancy on the cardiovascular system can persist for several months after delivery;[4,27] thus, the lack of longer-term follow-up could potentially confound our results.[34,35] Therefore future studies should consider a longer follow-up period.

CONCLUSIONS

Pregnancy outcomes in women with CHD-associated PH differed by PH severity, with patients with CHD and mild PH having outcomes similar to those of women with CHD and no PH. Multimodality assessment including BNP level and NYHA class on top of the PH severity may further provide useful risk stratification in pregnancy with PH. Follow-up with MDT and strict antenatal supervision may be protective in the care of women with CHD and increased risk of adverse maternal cardiac events.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Tables S1–S4

Figures S1–S14

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