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Pregnancy and cardiovascular diseases

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Pregnancy and cardiovascular diseases

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Short-Term Prediction of Preeclampsia in Chinese Women Using the Soluble fms-Like Tyrosine Kinase 1/Placental Growth Factor Ratio: A Sub-Analysis of the PROGNOSIS Asia Study

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The diagnosis of preeclampsia in China currently relies on limited clinical signs and unspecific laboratory findings. These are inadequate predictors of preeclampsia development, limiting early diagnosis and appropriate management. Previously, the Prediction of Short-Term Outcome in Pregnant Women with Suspected Preeclampsia Study (PROGNOSIS) and PROGNOSIS Asia demonstrated that a soluble fms-like tyrosine kinase 1 (sFlt-1)/placental growth factor (PlGF) ratio of ≤38 can be used to rule out preeclampsia within 1 week, with negative predictive values of 99.3 and 98.6%, respectively. This is an exploratory sub-analysis of the Chinese cohort (n = 225) of the PROGNOSIS Asia study. The primary objectives were to assess the predictive performance of using the sFlt-1/PlGF ratio to rule out preeclampsia within 1 week and to rule in preeclampsia within 4 weeks. The sFlt-1/PlGF ratio was also examined for short-term prediction of fetal adverse outcomes, maternal adverse outcomes, and time to delivery. The overall prevalence of preeclampsia was 17.3%. With the use of an sFlt-1/PlGF ratio of ≤38, the negative predictive value for ruling out preeclampsia within 1 week was 97.3% [95% confidence interval (CI), 93.8–99.1], with a sensitivity of 64.3% and specificity of 85.3%. With the use of an sFlt-1/PlGF ratio of >38, the positive predictive value for ruling in preeclampsia within 4 weeks was 35.0% (95% CI, 20.6–51.7), with a sensitivity of 50.0% and specificity of 86.8%. In the analyses of the sFlt-1/PlGF ratio and fetal adverse outcomes, the area under the receiver operating characteristic curve was 92.8% (95% CI, 83.5–98.7) for ruling out fetal adverse outcomes within 1 week and 79.9% (95% CI, 68.1–90.3) for ruling in fetal adverse outcomes within 4 weeks. An sFlt-1/PlGF ratio of >38 increased the likelihood of imminent delivery 3.3-fold compared with

a ratio of ≤38 [hazard ratio, 3.3 (95% CI, 2.1–5.1)]. This sub-analysis confirms the high predictive performance of the sFlt-1/PlGF ratio cutoff of 38 for short-term prediction of preeclampsia in Chinese women, which may help prevent unnecessary hospitalization of women with low risk of developing preeclampsia.

Keywords: soluble fms-like tyrosine kinase 1, placental growth factor, preeclampsia, prediction, China

INTRODUCTION

Preeclampsia is a heterogeneous, pregnancy-specific hypertensive disease with multisystem involvement (1). It affects 2–8% of pregnancies worldwide and approximately 1.9% of pregnancies in China (2–4). The relationship between ethnicity and the risk of preeclampsia is well-documented, with some studies reporting the morbidity of the Uygur 2.4 times higher than that of the Han nationality in China (5).

Preeclampsia is a major cause of perinatal and maternal morbidity and mortality (6), with an estimated 2.6 million stillbirths each year, of which 98% occur in low- and middle-income countries. In China, a stillbirth rate of 8.8 per 1,000 births was reported in 2016 (7).

Currently, diagnosis of preeclampsia relies on the presence of new-onset hypertension plus proteinuria, although both are in fact poor predictors of preeclampsia development (8, 9). Diagnosis of preeclampsia in China is largely based on limited clinical information and unspecific laboratory findings, due to a need for timely diagnosis and patient management (10). Consequently, the triage of Chinese women presenting with suspected preeclampsia is challenging (11). This inability to accurately predict preeclampsia may lead to the unnecessary hospitalization of women, or a failure to identify those women who develop preeclampsia, with increased risks for the fetus. A reliable method for the short-term prediction of preeclampsia in Chinese women is therefore needed.

An imbalance of circulating maternal levels of soluble fms-like tyrosine kinase 1 (sFlt-1) and placental growth factor (PlGF) is associated with preeclampsia development (12). The ratio of sFlt-1 to PlGF is elevated in pregnant women 4–5 weeks prior to and during the clinical onset of preeclampsia (13). The sFlt-1/PlGF ratio has also been shown to discriminate between different types of pregnancy-related hypertensive disorders when combined with other clinical biomarkers (14, 15). The Prediction of Short-Term Outcome in Pregnant Women with Suspected Preeclampsia Study (PROGNOSIS) and PROGNOSIS Asia studies have previously shown that an sFlt-1/PlGF ratio of ≤38 can rule out preeclampsia within 1 week, while a ratio of >38 can rule in preeclampsia within 4 weeks (16–18).

This exploratory sub-analysis of the PROGNOSIS Asia study was performed to assess the performance of the sFlt-1/PlGF ratio for short-term prediction of preeclampsia and pregnancy-related adverse events in Chinese women.

MATERIALS AND METHODS

Study Overview

PROGNOSIS Asia was a prospective, blinded, non-interventional, multicenter study that enrolled 764 women with suspected preeclampsia at 25 sites across Asia (China, Hong Kong, Japan, Singapore, South Korea, and Thailand) between December 2014 and December 2016; results of the primary analysis have been reported previously (18), as have results of an exploratory sub-analysis of the Japanese cohort (19). The Chinese cohort was enrolled at seven sites in mainland China between March 2015 and September 2016.

Local ethics committees and institutional review boards at each site approved the protocol prior to study initiation, and approval from the Human Genetic Resources Administration of China was obtained (May 2016). The study was performed in compliance with the International Conference on Harmonization guidelines for Good Clinical Practice and the principles of the Declaration of Helsinki, and all participants provided written informed consent.

Study Participants

Eligible participants included pregnant women ≥18 years of age, at gestational age 20 weeks + 0 days to 36 weeks + 6 days, with clinical suspicion of preeclampsia according to protocol-defined criteria, previously published by Bian et al. (18). Women who had manifest preeclampsia or a confirmed diagnosis of hemolysis, elevated liver enzymes, low platelet count (HELLP) syndrome; those with multiple pregnancies or a confirmed diagnosis of a fetal chromosomal abnormality; and those who had received treatment with an investigational medicine within 90 days before enrollment were excluded. Diagnostic criteria for preeclampsia and preeclampsia-related disorders were based on the International Society for the Study of Hypertension in Pregnancy guidelines (ISSHP) (9), as described in Zeisler et al. (16).

Study Procedures

Demographic information and medical history for each participant were collected at screening. Assessments were made at all study visits: visit 1 (baseline), visit 2 (7–14 days from baseline), visit 3 (24–32 days from baseline), at delivery, and postpartum. In addition, unscheduled visits occurred in the event of pregnancy complications. Clinical data were collected at all study visits and recorded in an electronic case report form, with regular monitoring.

Maternal serum samples (2 ml) were collected at visits 1–3 according to standard operating procedures and were stored

frozen until analysis. Samples were analyzed by an independent accredited laboratory (Covance Central Laboratory Service, Shanghai, China). Maternal serum concentrations of sFlt-1 and PlGF (both measured in picograms per milliliter) were determined using the fully automated Elecsys® sFlt-1 and PlGF immunoassays on cobas e analyzers (Roche Diagnostics, Mannheim, Germany) (20). To prevent results from influencing clinical decision making, sample measurements were performed after study completion.

Analysis Objectives/Endpoints

The primary objectives were to assess the performance of an Elecsys sFlt-1/PlGF ratio cutoff of ≤38 to predict the absence of preeclampsia within 1 week and a cutoff of >38 to predict the occurrence of preeclampsia within 4 weeks. Based on the results of PROGNOSIS and PROGNOSIS Asia, selected secondary objectives were investigated in this Chinese cohort in an exploratory manner. These secondary objectives included investigation of the sFlt-1/PlGF ratio for short-term prediction of fetal and maternal adverse outcomes (FAOs and MAOs), and assessment of the correlation between the sFlt-1/PlGF ratio and time to delivery. FAOs examined included perinatal/fetal death, delivery <34 weeks, fetal growth restriction, placental abruption, neonatal respiratory distress syndrome, necrotizing enterocolitis, intraventricular hemorrhage, hospitalization separate from the mother, admission to neonatal intensive care unit, hypoxia, neurologic injury, and asphyxia. MAOs were defined as any preeclampsia-related adverse outcome other than preeclampsia/eclampsia/HELLP syndrome, including maternal death, pulmonary edema, acute renal failure, and cerebral hemorrhage.

Statistical Analyses

A sample determination formula according to Pepe (21) was applied. Sample size calculations were based on the Schatzkin criterion and were performed for the entire study population of PROGNOSIS Asia (not for analyses in subsets). Data analysis followed a statistical analysis plan and used SAS 9.4 software (SAS, Cary, NC, USA), and R 3.2.2 and R 3.4.0 software (R Foundation, Vienna, Austria). All data were transferred to the sponsor for merging and analysis at the end of the study. The sFlt-1/PlGF ratio was calculated by the Roche biostatistics department (Penzberg, Germany). Descriptive statistics were reported as median and interquartile range (IQR) for continuous data, and as absolute and relative frequencies for count data. The predictive performance of the sFlt-1/PlGF ratio was assessed by estimating negative predictive value (NPV), positive predictive value (PPV), sensitivity, specificity, and area under the receiver operating characteristic (ROC) curve, each derived with a corresponding 95% confidence interval (CI). The impact of the sFlt-1/PlGF ratio on the remaining pregnancy duration at the time of blood sampling was estimated by Cox regression, dichotomized by sFlt-1/PlGF ratio status (≤38 vs. >38), and adjusted for gestational age and final preeclampsia status.

RESULTS

Analysis Population

Of the 250 women enrolled in the Chinese cohort, 225 (90%) were evaluable and included in the current analysis (**Supplementary Figure 1**). Median age at baseline and gestational age at baseline were comparable between women who developed preeclampsia and those who did not develop preeclampsia ($p = 0.488$ and $p = 0.327$, respectively; **Table 1**). Median body mass index and blood pressure were higher in women who developed preeclampsia than in those who did not develop preeclampsia ($p < 0.001$ and $p < 0.001$, respectively), whereas median gestational age at delivery and median height and weight of the neonate were lower in women who developed preeclampsia than in those who did not develop preeclampsia ($p < 0.001$, $p < 0.001$, and $p < 0.001$, respectively). The overall prevalence of preeclampsia was 17.3%, with 6.2% of women diagnosed within 1 week and 12.4% diagnosed within 4 weeks. The most common reasons for suspected preeclampsia were as follows: "new onset of hypertension" (54.7%), "new onset of protein in urine" (23.6%), and "abnormal uterine perfusion" (23.6%).

Short-Term Prediction of Preeclampsia

Median sFlt-1/PlGF ratios were elevated among women who developed preeclampsia within 1 week compared with women who did not develop preeclampsia within 1 week (151.68 vs. 7.18). The same trend was observed after 4 weeks (36.97 vs. 6.84) and overall (31.21 vs. 6.43) (**Figure 1A**). The sFlt-1/PlGF ratio showed moderate sensitivity and high specificity for ruling out preeclampsia within 1 week (ratio ≤38) and ruling in preeclampsia within 4 weeks (ratio >38) (**Table 2**). Based on an sFlt-1/PlGF ratio of ≤38, the NPV for ruling out preeclampsia within 1 week was 97.3% (95% CI, 93.8–99.1). The area under the ROC curve for the sFlt-1/PlGF ratio ruling out preeclampsia within 1 week was 75.6% (95% CI, 58.1–91.2) (**Figure 1B**). With the use of an sFlt-1/PlGF ratio of >38, the PPV for ruling in preeclampsia within 4 weeks was 35.0% (95% CI, 20.6–51.7). The area under the ROC curve for the sFlt-1/PlGF ratio ruling in preeclampsia within 4 weeks was 72.7% (95% CI, 59.8–84.2) (**Figure 1B**).

Short-Term Prediction of Pregnancy-Related Adverse Outcomes

Two hundred twenty-one participants were eligible for analysis of the sFlt-1/PlGF ratio and prediction of FAOs. FAOs occurred in eight women within 1 week and 28 women within 4 weeks. The sFlt-1/PlGF ratio was higher in women with ≥1 FAO than in women with no FAOs (**Table 3**), with the highest sFlt-1/PlGF ratios observed in women who both were diagnosed with preeclampsia and experienced an FAO; this trend was consistent at 1 and 4 weeks (**Figures 2A,B**). In the ROC curve analysis, the area under the curve was 92.8% (95% CI, 83.5–98.7) for ruling out FAOs within 1 week and 79.9% (95% CI, 68.1–90.3) for ruling in FAOs within 4 weeks (**Figures 2C,D**). None of the participants included in the Chinese cohort experienced an MAO (as defined by the study protocol), which

TABLE 1 | Participant demographics and characteristics at baseline for the whole cohort and according to preeclampsia status.

Characteristic[a,b]	All women ($N = 225$)	No preeclampsia at any time ($n = 186$)	Preeclampsia at any time ($n = 39$)
Age, years	31.0 (28.0–34.0)	31.0 (29.0–34.0)	31.0 (28.0–34.0)
Gestational age of pregnancy at baseline, weeks	30.6 (26.7–33.7)	30.5 (26.7–34.0)	30.9 (26.3–32.3)
Gestational age of pregnancy at delivery, weeks	38.1 (36.7–39.1)	38.4 (37.1–39.3)	36.3 (34.3–37.4)
Blood pressure at baseline, mmHg			
Systolic	138.0 (125.0–148.0)	136.5 (121.0–146.0)	146.0 (135.0–160.0)
Diastolic	91.0 (81.0–98.0)	90.0 (78.0–97.0)	94.0 (90.0–107.0)
Pre-pregnancy BMI, kg/m^2	23.8 (20.8–26.5)	23.4 (20.7–25.8)	26.2 (23.3–30.5)
Reasons for suspected preeclampsia, *n* (%)[c]			
New onset of hypertension	123 (54.7)	102 (54.8)	21 (53.8)
Aggravation of preexisting hypertension	30 (13.3)	21 (11.3)	9 (23.1)
New onset of protein in urine	53 (23.6)	38 (20.4)	15 (38.5)
Aggravation of preexisting proteinuria	3 (1.3)	1 (0.5)	2 (5.1)
Epigastric pain	0	0	0
Visual disturbances	0	0	0
Abnormal uterine perfusion	53 (23.6)	45 (24.2)	8 (20.5)
Partial HELLP syndrome	7 (3.1)	6 (3.2)	1 (2.6)
Height of neonate, cm	49 (47–50)	50 (48–50)	47 (44–50)
Weight of neonate, g	2,950 (2,440–3,350)	2,980 (2,600–3,390)	2,310 (1,800–3,080)

BMI, body mass index; HELLP, hemolysis, elevated liver enzymes, low platelet count.

[a]Data are reported as median (interquartile range), unless stated otherwise.

[b]p-values were calculated using the Mann–Whitney U-test for continuous variables and Fisher's exact test for categorical variables. Statistically significant differences were observed between women who did not develop preeclampsia at any time and women who developed preeclampsia for the following characteristics: gestational age at delivery ($p < 0.001$), systolic blood pressure at baseline ($p < 0.001$), diastolic blood pressure at baseline ($p < 0.001$), maximum systolic blood pressure ($p < 0.001$), maximum diastolic blood pressure ($p < 0.001$), pre-pregnancy BMI ($p < 0.001$), height of neonate ($p < 0.001$), weight of neonate ($p < 0.001$), and new onset of protein in urine ($p = 0.022$). For the remaining characteristics, p-values were as follows between the two groups: age ($p = 0.488$), gestational age at visit 1 ($p = 0.327$), new onset of hypertension ($p = 1$), aggravation of preexisting hypertension ($p = 0.067$), aggravation of preexisting proteinuria ($p = 0.078$), suspected intrauterine growth restriction or abnormal uterine perfusion ($p = 0.684$), and partial HELLP syndrome ($p = 1$).

[c]Some women had suspected preeclampsia for more than one reason.

did not allow for analysis of the sFlt-1/PlGF ratio to predict these outcomes.

Correlation Between the Soluble fms-Like Tyrosine Kinase 1/Placental Growth Factor Ratio and Time to Delivery

Data for analysis of sFlt-1/PlGF ratio and time to delivery were available for 223 eligible participants. Higher sFlt-1/PlGF ratios were associated with increasingly shorter pregnancy duration leading to preterm delivery (**Figure 3**), both for women who developed preeclampsia and for those who did not. With the use of Cox regression analysis, the likelihood of imminent delivery (day of test) was 3.3-fold (95% CI, 2.1–5.1) higher in women with an sFlt-1/PlGF ratio >38 vs. ≤38, irrespective of preeclampsia status.

DISCUSSION

The present sub-analysis validates the predictive value of the sFlt-1/PlGF ratio cutoff of 38 for short-term prediction of preeclampsia, FAOs, and pre-term delivery in Chinese women with clinically suspected preeclampsia. The high NPV [97.3% (95% CI, 93.8–99.1)] of the sFlt-1/PlGF ratio (cutoff ≤38) observed in this sub-analysis allows clinicians to rule out preeclampsia within 1 week in Chinese women with a high degree of confidence, thus supporting clinical decision making on whether to hospitalize patients or not. This has the potential to reduce unnecessary hospitalizations and interventions for women at low risk of preeclampsia, who may instead be monitored and managed in an outpatient setting. The sFlt-1/PlGF ratio >38 provides a PPV of 35.0% (95% CI, 20.6–51.7) for ruling in preeclampsia within 4 weeks in Chinese women. This is higher than that of other predictors such as high blood pressure, which have been shown to have a PPV of 20% for detecting preeclampsia (22).

For the first time, PROGNOSIS Asia demonstrated the value of determining the sFlt-1/PlGF ratio for the short-term prediction of preeclampsia and pregnancy-related adverse outcomes in Asian women with signs and symptoms of preeclampsia (18). The Chinese cohort showed findings consistent with the overall PROGNOSIS Asia study population (18). Baseline characteristics were comparable between the Chinese cohort and the overall population; however, prevalence of preeclampsia was higher in the Chinese cohort (17.3%) compared with the overall population (14.4%). The NPVs for ruling out preeclampsia within 1 week in the Chinese cohort

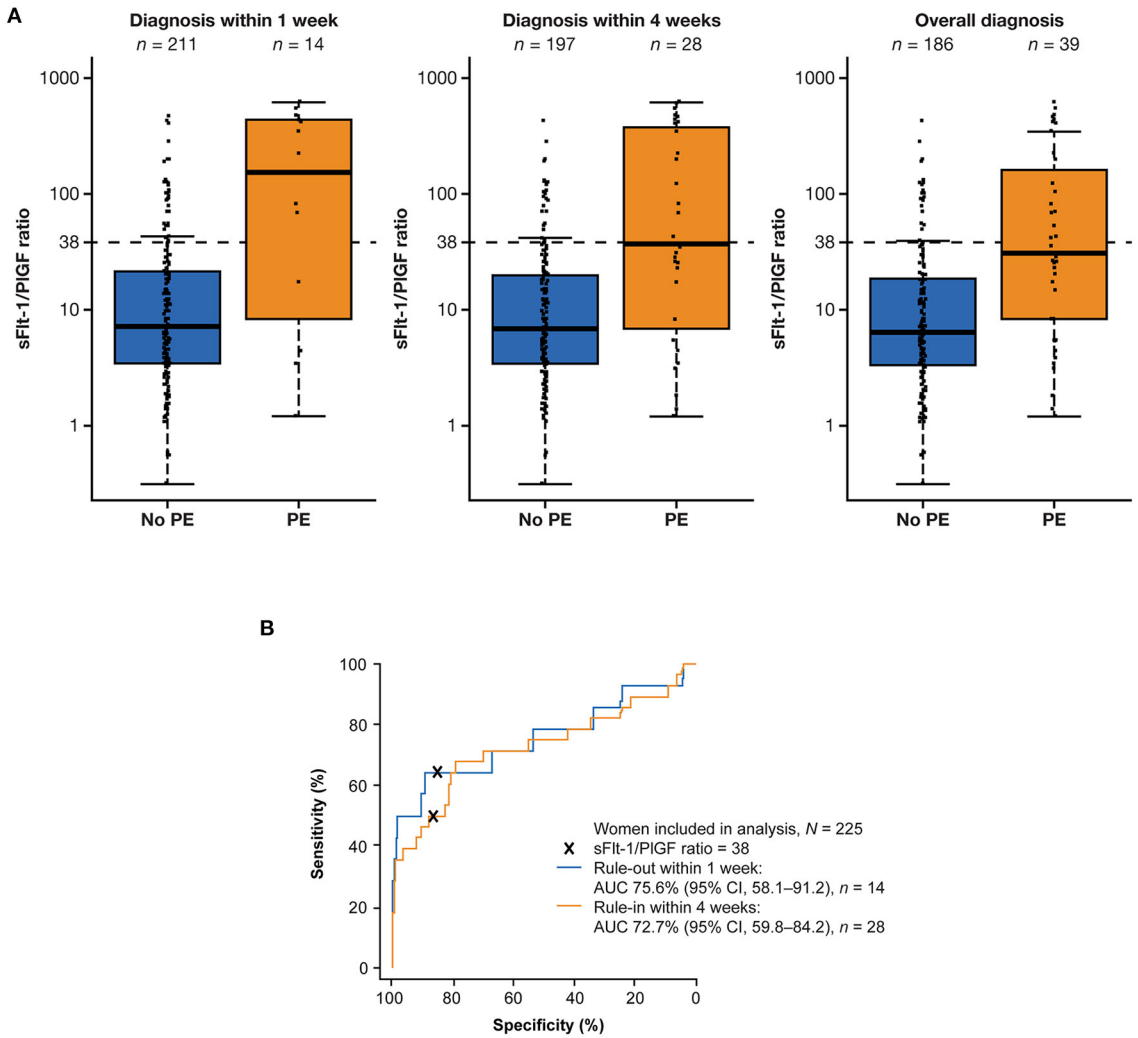

FIGURE 1 | Performance of the sFlt-1/PlGF ratio for predicting preeclampsia within 1 and 4 weeks. **(A)** Distribution of sFlt-1/PlGF ratios at baseline for participants who developed or did not develop preeclampsia within 1 week, within 4 weeks, and overall.[a] **(B)** Performance of the ratio for ruling out preeclampsia within 1 week (blue) and ruling in preeclampsia within 4 weeks (orange). [a]The boxes represent the first and third quartiles and the median value. The whiskers represent values that are 1.5 × the IQR or shorter in cases where the minimal/maximal value lies within 1.5 × the IQR in log scale. AUC, area under the curve; CI, confidence interval; IQR, interquartile range; PE, preeclampsia; PlGF, placental growth factor; sFlt-1, soluble fms-like tyrosine kinase 1.

and overall population were 97.3 and 98.6%, respectively. While the PPV for ruling in preeclampsia within 4 weeks was higher in the Chinese cohort (35.0%) vs. the overall population (30.3%), this may be explained by a higher prevalence of preeclampsia in the Chinese cohort compared with overall prevalence (17.3 vs. 14.4%, respectively). The area under the ROC curve for the Chinese cohort and overall population was 92.8 and 91.0%, respectively, for ruling out any FAO within 1 week, and 79.9 and 83.1%, respectively, for ruling in any FAO within 4 weeks. The risk of imminent delivery in women with an sFlt-1/PlGF ratio >38 vs. ≤38 was also comparable between cohorts, with a 3.3-fold and 3.5-fold higher risk observed in the Chinese cohort and overall population, respectively. For all the above results, the 95% CIs in the Chinese cohort overlapped with those from the overall population.

Findings from the Chinese cohort were also consistent with those of an exploratory sub-analysis of the Japanese cohort from PROGNOSIS Asia (19). In the Japanese cohort, overall prevalence of preeclampsia was lower compared with the Chinese cohort (13.3 vs. 17.3%). Median blood pressure at baseline for women who developed preeclampsia at any time was also lower in the Japanese cohort (systolic, 138 vs. 146 mmHg; diastolic, 84 vs. 94 mmHg), while median age was higher in the Japanese cohort compared with the Chinese cohort (35.0 vs. 31.0 years).

The NPV for ruling out preeclampsia within 1 week in the Chinese cohort was lower than that of the Japanese cohort (97.3 vs. 100%), while the PPV for ruling in preeclampsia within 4

TABLE 2 | Performance of the sFlt-1/PlGF ratio using a cutoff of 38 for short-term prediction of preeclampsia.

Preeclampsia	NPV, % (95% CI)	PPV, % (95% CI)	Sensitivity, % (95% CI)	Specificity, % (95% CI)
Within 1 week	**97.3 (93.8–99.1)**[a]	22.5 (10.8–38.5)	64.3 (35.1–87.2)	85.3 (79.8–89.8)
Within 4 weeks	92.4 (87.6–95.8)	**35.0 (20.6–51.7)**[a]	50.0 (30.6–69.4)	86.8 (81.3–91.2)

CI, confidence interval; NPV, negative predictive value; PlGF, placental growth factor; PPV, positive predictive value; sFlt-1, soluble fms-like tyrosine kinase 1.
[a]*Primary study objectives; for rule out of preeclampsia within 1 week, an sFlt-1/PlGF ratio of ≤38 was used. For rule in of preeclampsia within 4 weeks, an sFlt-1/PlGF ratio of >38 was used.*

TABLE 3 | Distribution of sFlt-1/PlGF ratios by FAO status within 1 and 4 weeks in all women and by preeclampsia status.[a]

FAO status (without/with preeclampsia[b])	*N*	sFlt-1/PlGF ratio, median (IQR)
FAO within 1 week	8	208.6 (105.8–431.3)
Women without preeclampsia within 1 week	5	124.8 (86.9–195.9)
Women with preeclampsia within 1 week	3	435.3 (221.3–611.5)
No FAO within 1 week	213	7.2 (3.4–21.8)
Women without preeclampsia within 1 week	202	7.1 (3.4–20.8)
Women with preeclampsia within 1 week	11	67.7 (4.4–417.4)
FAO within 4 weeks	28	119.4 (17.0–310.7)
Women without preeclampsia within 4 weeks	18	67.9 (5.2–124.8)
Women with preeclampsia within 4 weeks	10	376.2 (198.1–435.3)
No FAO within 4 weeks	193	6.8 (3.4–19.7)
Women without preeclampsia within 4 weeks	176	6.5 (3.4–18.2)
Women with preeclampsia within 4 weeks	17	22.7 (4.4–42.7)

FAO, fetal adverse outcome; HELLP, hemolysis, elevated liver enzymes, low platelet count; IQR, interquartile range; PlGF, placental growth factor; sFlt-1, soluble fms-like tyrosine kinase 1.
[a]*221 participants from China were eligible for this analysis.*
[b]*Preeclampsia/eclampsia/HELLP syndrome.*

weeks was higher in the Chinese cohort compared with the Japanese cohort (35.0 vs. 32.4%). As previously stated, this may be attributed to the higher prevalence of preeclampsia in the Chinese cohort compared with the Japanese cohort (17.3 vs. 13.3%). The area under the ROC curve for ruling out any FAO within 1 week was lower in the Chinese cohort compared with the Japanese cohort (92.8 vs. 93.0%), while risk of imminent delivery in women with an sFlt-1/PlGF ratio >38 vs. ≤38 was higher in the Chinese cohort (3.3-fold vs. 2.8-fold). Again, for all of the above results, 95% CIs in the Chinese cohort overlapped with those from the Japanese cohort.

Our findings were also in line with those of the PROGNOSIS study, in which a 17.8% incidence rate of preeclampsia and/or HELLP syndrome was reported in the validation cohort (74.5% Caucasian) (16). Baseline characteristics were comparable between the Chinese cohort and the PROGNOSIS validation cohort. Moreover, predictive performance of the sFlt-1/PlGF ratio was similar between the PROGNOSIS validation cohort and the Chinese cohort for NPV for ruling out preeclampsia within 1 week (99.3 vs. 97.3%), PPV for ruling in preeclampsia within 4 weeks (36.7 vs. 35.0%), and area under the ROC curve (1 week, 86.1 vs. 75.6%; 4 weeks, 82.3 vs. 72.7%).

The present findings are also consistent with data from the randomized Interventional Study Evaluating the Short-Term Prediction of Preeclampsia/Eclampsia In Pregnant Women With Suspected Preeclampsia (INSPIRE) study, which examined the clinical utility of the sFlt-1/PlGF ratio using a cutoff of 38 (23). The NPV for ruling out preeclampsia within 1 week in the present analysis was 97.3% compared with 100% in INSPIRE (with standard clinical management plus sFlt-1/PlGF ratio; 99.2% using the ratio only).

The findings of this analysis are applicable to Chinese women with clinically suspected preeclampsia and are supported by previous studies demonstrating the predictive value of the sFlt-1/PlGF ratio using a cutoff of 38 in Asian and Caucasian women (16, 18). The potential value of the sFlt-1/PlGF ratio may also extend beyond the prediction of preeclampsia, with other investigators reporting the utility of the ratio for aiding in the diagnosis of early-onset preeclampsia in Chinese women (5, 10).

A strength of this sub-analysis was the use of a well-defined cohort recruited across multiple centers in China. Furthermore, diagnostic criteria were based on ISSHP criteria, ensuring comparability of study results with the PROGNOSIS and PROGNOSIS Asia studies (16). However, our analysis has some limitations. As an exploratory sub-analysis of the PROGNOSIS Asia study, the analysis was not powered for the

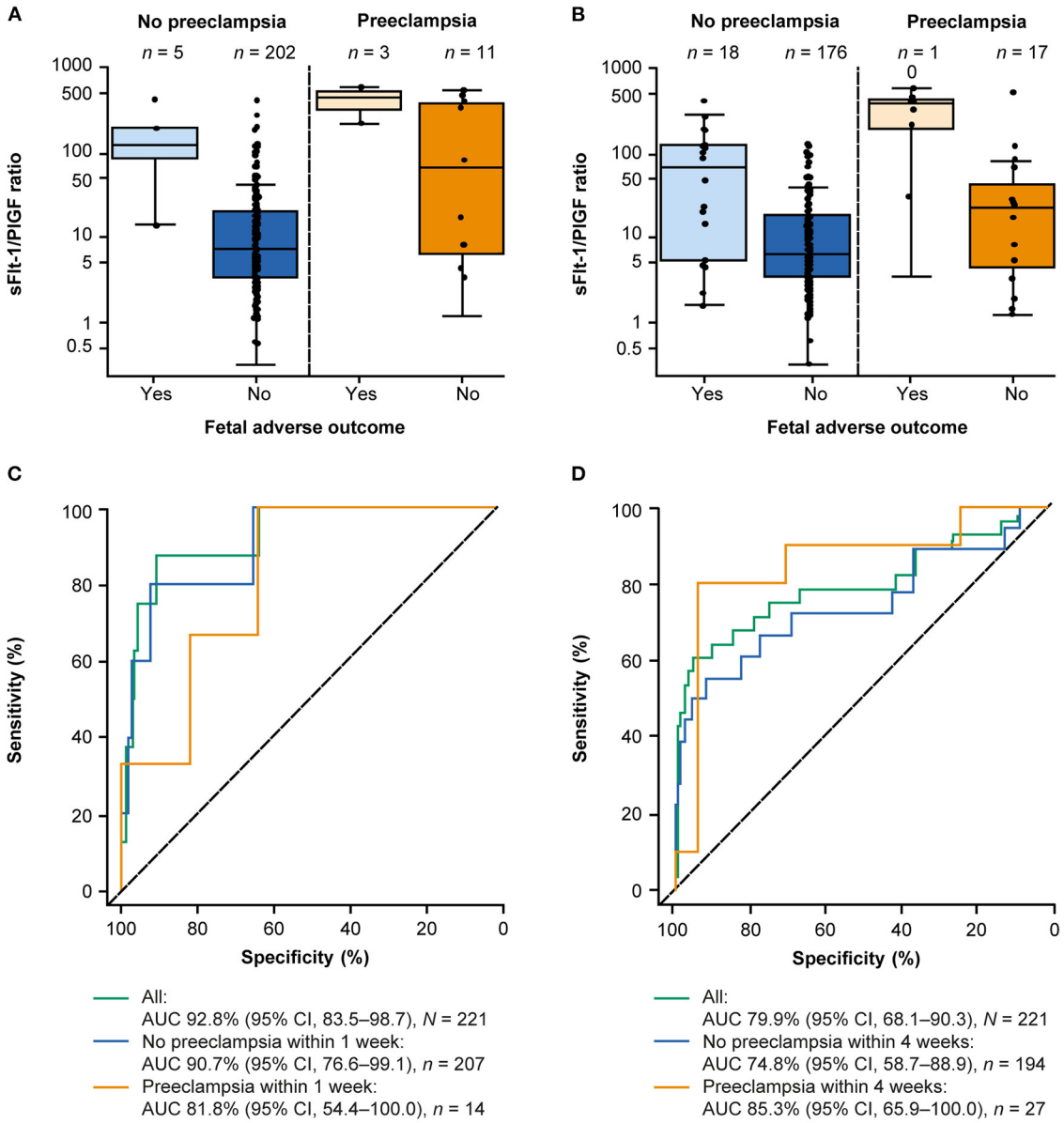

FIGURE 2 | Performance of the sFlt-1/PlGF ratio for predicting FAOs within 1 and 4 weeks.[a] **(A)** Distribution of the sFlt-1/PlGF ratio at baseline according to FAO status and preeclampsia status within 1 week and **(B)** within 4 weeks.[b] **(C)** Performance of the sFlt-1/PlGF ratio for short-term prediction of FAOs within 1 week and **(D)** within 4 weeks. [a]A total of 221 participants from China were eligible for this analysis. [b]The boxes represent the first and third quartiles and the median value. The whiskers represent values that are 1.5 × the IQR or shorter in cases where the minimal/maximal value lies within 1.5 × the IQR in log scale. AUC, area under the curve; CI, confidence interval; FAO, fetal adverse outcome; IQR, interquartile range; PlGF, placental growth factor; sFlt-1, soluble fms-like tyrosine kinase 1.

Chinese cohort presented but rather for the primary analysis of PROGNOSIS Asia. Herein, we used the Elecsys sFlt-1 and PlGF immunoassays to apply the sFlt-1/PlGF ratio cutoff of 38 to predict preeclampsia, but the use of assays from other manufacturers may require a different optimal cutoff. For example, it has been reported that cutoffs for the Elecsys sFlt-1/PlGF ratio are not transferrable to the Brahms Kryptor sFlt-1/PlGF immunoassay (24, 25). In addition, PROGNOSIS Asia was an observational, rather than interventional, study. Further studies should evaluate the real-world utility of the sFlt-1/PlGF ratio for predicting preeclampsia in China.

CONCLUSIONS

This sub-analysis of the Chinese cohort of the PROGNOSIS Asia study confirms the high predictive performance of the Elecsys sFlt-1/PlGF ratio cutoff of 38 for short-term prediction of preeclampsia in Chinese women. The high NPV of 97.3% may

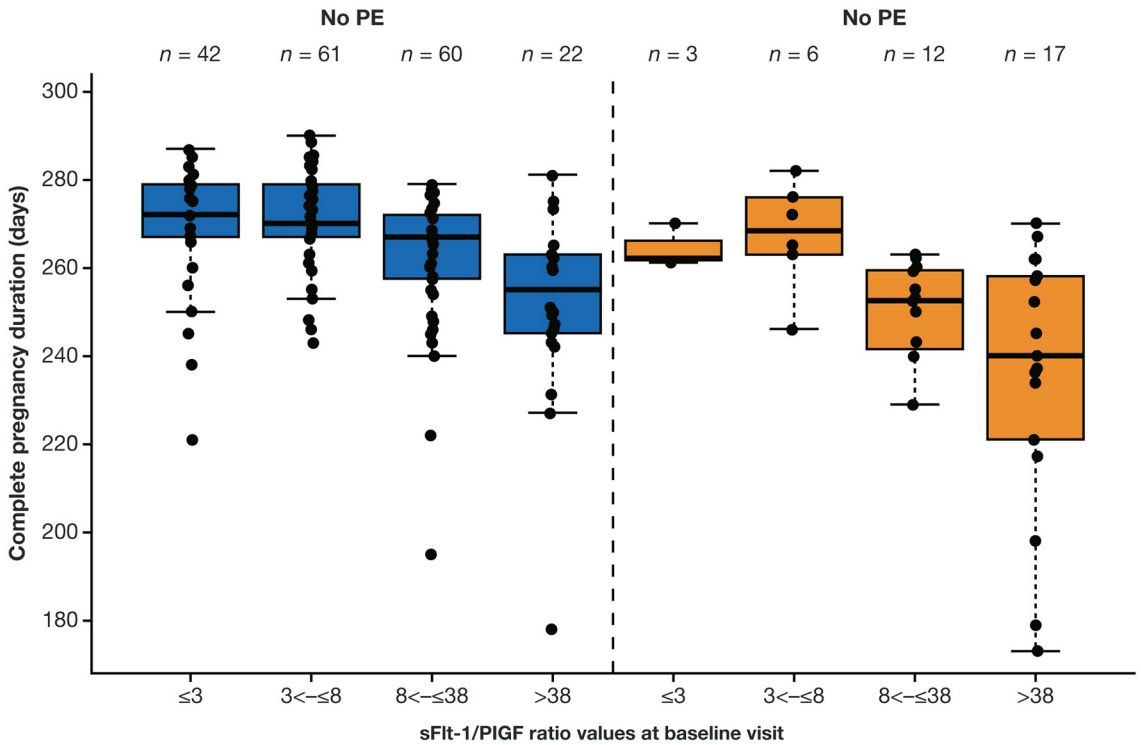

FIGURE 3 | Distribution of complete pregnancy duration according to sFlt-1/PlGF ratio at baseline visit by overall preeclampsia status.[a,b] [a]A total of 223 participants from China were eligible for this analysis. [b]The boxes represent the first and third quartiles and the median value. The whiskers represent values that are IQR or shorter in cases where the minimal/maximal value lies within 1.5 × the IQR. The boxes represent the median and IQR in log scale. IQR, interquartile range; PE, preeclampsia; PlGF, placental growth factor; sFlt-1, soluble fms-like tyrosine kinase 1.

enable physicians to rule out preeclampsia within 1 week, which may help to prevent unnecessary hospitalization of women with suspected preeclampsia.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from Roche Diagnostics International Ltd, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are, however, available from the authors upon reasonable request and with permission of Roche Diagnostics International Ltd.

AUTHOR CONTRIBUTIONS

JG, XH, WD, XD, WG, HS, and ZW were involved in collection and interpretation of data. AD, SG, and MH were involved in study design and concept development, analysis, and interpretation of data. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2021.602560/full#supplementary-material

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Conflict of Interest: AD and SG are employees of Roche Diagnostics GmbH. MH is an employee of Roche Diagnostics International Ltd and holds stock in F. Hoffmann-La Roche. MH also reports being an inventor of patents related to sFlt-1/PlGF or endoglin/PlGF ratio to rule out onset of preeclampsia in pregnant women within a certain time period PCT/EP2013/063115 and the dynamic of sFlt-1 or endoglin/PlGF ratio as indicator for imminent preeclampsia and HELLP syndrome PCT/EP2012/072157.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Multidisciplinary Team Managements and Clinical Outcomes in Patients With Pulmonary Arterial Hypertension During the Perinatal Period

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Background: Pulmonary arterial hypertension (PAH) patients with pregnancy have high maternal mortality. This study aimed to provide clinical evidence with multidisciplinary team (MDT) management and to evaluate the clinical outcomes in PAH patients during the perinatal period.

Methods: We conducted a retrospective evaluation of PAH patients pregnant at the First Affiliated Hospital of Chongqing Medical University between May 2015 and May 2021.

Results: Twenty-two patients (24 pregnancies) were included in this study and received MDT management, and 21 pregnancies chose to continue pregnancy with cesarean section. Nine (37.5%) were first-time pregnancies at 27.78 ± 6.16 years old, and 15 (62.5%) were multiple pregnancies at 30.73 ± 3.71 years old. The average gestational week at hospitalization and delivery were 29.38 ± 8.63 weeks and 32.37 ± 7.20 weeks, individually. Twenty-one (87.5%) pregnancies received single or combined pulmonary vasodilators. The maternal survival rate of PAH patients reached 91.7%. Fifteen (62.5%) pregnancies were complicated with severe adverse events. Patients with complicated adverse events showed lower percutaneous oxygen saturation (SpO_2), lower albumin, lower fibrinogen, higher pulmonary artery systolic pressure (PASP), higher blood pressure, longer activated partial thromboplastin time, and longer coagulation time. Fourteen (66.7%) pregnancies with cesarean sections were prematurely delivered and 85.7% newborns who survived after the operation remained alive.

Conclusion: The survival rate of parturients with PAH was improved in relation to MDT and pulmonary vasodilator therapy during the perinatal period compared with previous studies. SpO_2, albumin, PASP, blood pressure, and coagulation function should be monitored carefully in PAH patients during pregnancy.

Keywords: pulmonary arterial hypertension, perinatal period, multidisciplinary team, pregnancy, outcomes

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a severe disease with the main pathological change being elevated pulmonary vascular resistance, which often leads to right ventricular failure and death (1). The population with a high incidence includes females of childbearing age, and the first clinical manifestations may appear in pregnancy (2). Extensive physiological changes during pregnancy and delivery can exacerbate right ventricular failure in PAH patients (3), leading to high maternal mortality (between 25 and 56%) and poor neonatal outcomes (4–6). Although pregnancy has been prohibited in the European Society of Cardiology (ESC) PAH guidelines (7), some women with PAH insist on pregnancy despite the potential risks.

Advances in medical management have gradually improved the outcomes of PAH patients with pregnancy, but maternal mortality remains high (16–30%) (8, 9). The current guidelines still recommend strict contraception for PAH patients, and early termination is strongly recommended for PAH with pregnancy (7). The management of PAH patients during the perinatal period is heterogeneous in various medical centers, and the evidence of delivery modes, PAH targeted therapy, hemodynamic management, and the use of oxytocin are also unclear (7). Previous studies have suggested early clinical deterioration, severe right ventricular failure, brain natriuretic peptide elevation, and World Health Organization function class III or IV symptoms as high risk factors for maternal outcome (10–12). This study aimed to provide clinical evidence with multidisciplinary team (MDT) management and to evaluate the maternal and infant clinical outcomes in PAH patients during the perinatal period.

METHODS

Patients

We identified PAH patients who were pregnant at the First Affiliated Hospital of Chongqing Medical University China between May 2015 and May 2021. Electronic and paper medical records of all the patients identified by the query were reviewed independently by two investigators (T. T. Shu and P. P. Feng). Inclusion in the study was predicated on a clinical diagnosis of PAH confirmed by clinical history, physical examination, right-sided heart catheterization (RHC, at the time of admission or within the preceding 5 years), or ultrasound cardiogram (UCG) (1). Patients with preexisting cardiomyopathy, left ventricular ejection fraction <40%, or mitral or aortic valve disease were excluded. Severe PAH was defined as systolic pulmonary artery pressure (PASP) ≥70 mmHg based on the highest measured value during pregnancy (9).

Data Extraction

Data extraction included patient demographic data, including age, insurance, gestational age, expenses, etiology of PAH, comorbidities, and PAH targeted therapy before, during, and after pregnancy. The clinical baseline characteristics included clinical symptoms, blood pressure (BP), heart rate, percutaneous oxygen saturation (SpO_2) as measured by finger oximetry, laboratory tests, UCG, and electrocardiogram reports. Perinatal data included delivery mode, the timing of delivery, type of anesthesia, medications, intraoperative bleeding, and intraoperative vital signs. Maternal and neonatal outcomes were collected, including Apgar score, neonatal weight, and referral. Severe adverse events (SAEs) were defined as death, heart failure (HF), respiratory failure (RF), and infection. The patients were divided into the SAE group and without SAE group.

Statistical Analysis

The clinical baseline characteristics of all included pregnancies were descriptive in detail, and they were subgrouped and summarized according to underlying diseases and number of pregnancies. Data are presented as the mean ± standard deviation (SD) for parametric data, and the differences were compared between subgroups. A comparison of continuous parameters was performed using Student's *t*-test. Dichotomous variables were analyzed using χ^2 or Fisher's exact test. The difference analysis was performed by SPSS 22.0 software. A P-value < 0.05 was considered statistically significant.

RESULTS

Baseline Characteristics

Twenty-two female patients (24 pregnancies) with PAH were identified in this study. Two patients were pregnant twice during the study. All pregnancies were natural pregnancies, and there were no medical conceptions. The baseline characteristics are shown in **Table 1**. Eighteen (82%) patients were diagnosed with PAH associated with congenital heart disease (PAH-CHD), three (14%) were idiopathic PAH (IPAH), and one (4%) was PAH associated with connective tissue disease (PAH-CTD). Among these patients, five were diagnosed with PAH before pregnancy, and four received pulmonary vasodilator therapy in advance. Of the 24 pregnancies, nine (37.5%) were first-time pregnancies at 27.78 ± 6.16 years old, and 15 (62.5%) were multiple pregnancies at 30.73 ± 3.71 years old. The average gestational week at hospitalization was 29.38 ± 8.63 weeks. Comorbidities included subclinical hypothyroidism (2), hypothyroidism (1), antiphospholipid syndrome (1), hysteromyoma (1), diabetes (1), colon cancer (1), and uremia (1). There was no significant difference in baseline characteristics among all subgroups according to PAH etiology and gravidity history ($P > 0.05$, **Supplementary Table S1**).

Clinical symptoms on admission are shown in **Supplementary Table S2**, including shortness of breath (20), decreased exercise tolerance (19), palpitation (5), cyanosis (5), dyspnea in the semireclining position (4), acropachy (2), hemoptysis (2), edema (2), thorcalgia (1), syncope (1), and asymptomatic (2). Twelve (50%) of the 24 pregnancies had electrocardiographic abnormalities on admission, including sinus tachycardia (8), right bundle branch block (5), and left anterior fascicular block (2). Eleven patients had PAH-CHD (57.9%), and one had PAH-CTD. All patients underwent UCG examination after admission, and only 7 (30%) underwent RHC within the preceding 5 years. The echocardiographic or RHC

TABLE 1 | Baseline characteristics and management of PAH patients with pregnancy.

Patients	PAH age, y	Pregnancy age, y	GP history	Etiology	ES	NYHA class	BMI, kg/m^2	BP, mmHg	HR, bpm	PVs therapy before pregnancy		PVs therapy during pregnancy			Comorbidity
										Medicine	Start time, y	Medicine	Dose**	Start time, wk	
No. 1	30	30	G2P0	CHD (VSD)	Yes	IV	20.31	181/110	94	–	–	Treprostinil & Tadalafil	20 ng/kg/min 10 mg qd	32 32	Subclinical hypothyroidism
No. 2	29	29	G1P0	CHD (VSD)	Yes	III	17.63	102/76	107	–	–	Treprostinil	20 ng/kg/min	29	–
No. 3	31	31	G3P0	CTD	–	III–IV	21.09	92/68	79	–	–	Treprostinil & Tadalafil	20 ng/kg/min 10 mg qd	35 35	Hypothyroidism
No. 4	28	28	G1P0	IPAH	–	II–III	19.72	91/61	83	–	–	Treprostinil & Tadalafil	20 ng/kg/min 10 mg qd	14 14	–
No. 4*	28	30	G2P0	IPAH	–	II	22.49	104/65	80	Treprostinil, Tadalafil	28	Treprostinil & Tadalafil	20 ng/kg/min 10 mg qd	26 26	Hypothyroidism
No. 5	40	40	G1P0	CHD (ASD)	No	II	26.44	169/101	90	–	–	Treprostinil	20ng/kg/min	21	APS
No. 6	24	31	G3P0	CHD (VSD)	Yes	II–III	18.82	98/55	95	Sildenafil, Bosentan, Vardenafil, Ambrisentan, Tadalafil	25	Treprostinil & Tadalafil	20 ng/kg/min 10 mg bid	32 0	–
No. 7	30	30	G4P1	CHD (CCTGA+SV)	–	IV	25.78	136/84	100	–	–	Treprostinil	20 ng/kg/min	30	–
No. 8	25	25	G1P0	CHD (VSD)	Yes	II	20.45	121/81	100	–	–	Treprostinil	20 ng/kg/min	34	–
No. 9	36	36	G2P1	CHD (VSD)	No	II	25.81	107/63	96	–	–	Treprostinil	20 ng/kg/min	36	Hysteromyoma
No. 10	31	31	G3P1	CHD (ASD)	No	III	33.30	118/84	92	–	–	Treprostinil	20 ng/kg/min	36	–
No. 11	30	30	G3P1	CHD (ASD)	No	II	21.10	107/65	97	–	–	Treprostinil & Tadalafil	20 ng/kg/min 10 mg qd	27 27	–
No. 12	20	20	G1P0	CHD (ASD)	Yes	II	25.44	134/84	110	–	–	–	–	–	–
No. 13	22	22	G1P0	CHD (PDA)	–	III–IV	26.56	122/67	95	–	–	–	–	–	–
No. 14	18	23	G1P0	CHD (VSD)	No	II	17.30	110/52	69	–	–	–	–	–	
No. 14*	18	28	G2P0	CHD (VSD)	Yes	III–IV	22.96	132/77	110	Beraprost Sodium, Bosentan	23	Treprostinil & Tadalafil	20 ng/kg/min 10 mg qd	30 0	–
No. 15	38	38	G8P1	CHD (ASD)	No	II	33.59	128/57	88	–	–	–	–	–	Diabetes
No. 16	21	26	G3P0	CHD (PDA)	Yes	II	22.86	108/68	80	Bosentan, Sildenafil, Treprostinil	21	Treprostinil & Tadalafil	20 ng/kg/min 10 mg qd	33 33	–

(Continued)

TABLE 1 | Continued

Patients	PAH age, y	Pregnancy age, y	GP history	Etiology	ES	NYHA class	BMI, kg/m^2	BP, mmHg	HR, bpm	PVs therapy before pregnancy		PVs therapy during pregnancy			Comorbidity
										Medicine	Start time, y	Medicine	Dose**	Start time, wk	
No. 17	25	25	G3P1	IPAH	–	II–III	24.46	116/78	79	–	–	Treprostinil		31	Colon cancer
No. 18	30	30	G4P1	CHD (VSD)	No	IV	21.23	122/75	122	–	–	Sildenafil	20 mg tid	31	–
No. 19	37	37	G3P1	IPAH	–	IV	33.06	142/86	96	–	–	–	–	–	–
No. 20	32	32	G1P1	CHD (ASD)	No	III	24.84	155/101	103	–	–	–	–	–	Uremia
No. 21	28	28	G2P1	CHD (ASD)	No	I	31.20	106/57	102	–	–	–	–	–	–
No. 22	31	31	G1P0	CHD (ASD)	No	I	23.30	104/65	80	–	–	Treprostinil & Sildenafil	20 ng/kg/min 10 mg bid	12 16	–

PAH, pulmonary arterial hypertension; y, years old; GP history, gravidity and parity history; CHD, congenital heart disease; ASD, atrial septal defect; VSD, ventricular septal defect; CTD, connective tissue disease; IPAH, idiopathic pulmonary arterial hypertension; CCTGA, corrected transposition of great arteries; SV, single ventricle; PDA, patent ductus arteriosus; ES, eisenmenger syndrome; NYHA, New York Heart Association; BMI, body mass index; BP, blood pressure; HR, heart rate; bpm, beats per minute; PVs, pulmonary vasodilators; qd, once daily; bid, twice daily; tid, three times daily; wk, week; APS, antiphospholipid syndrome.

**The second pregnancy during the study period.*

***Treprostinil was titrated gradually from a low dose to a maintenance dose according to the instructions.*

parameters at the time of diagnosis of included PAH patients are shown in **Supplementary Table S3**.

The hospital admission indicators before termination of pregnancy or delivery are shown in **Table 2**. The average value of SpO_2 was 92.54% ± 9.4%, PASP was 73.74 ± 27.35 mmHg, and Barthel index was 90.00 ± 15.11 (**Supplementary Table S4**). The SpO_2 level in two patients was <70% in the non-oxygenated state. The difference in the Barthel index in disease subgroups was significant ($P < 0.05$), and the other indicators did not differ among the subgroups.

Managements and Delivery

The included patients received medical care from a MDT consisting of PAH physician experts, obstetricians, intensive care unit (ICU) physicians, anesthesiologists, neonatologists, and specialized ICU nurses. All 24 pregnancies were notified of high risk after admission and recommended termination of pregnancy. The average gestational week of termination or delivery was 32.37 ± 7.20 weeks. A total of three patients chose to terminate their pregnancy through medical induction within 20 weeks of gestation (**Table 3**). Twenty-one cases chose to continue their pregnancy for cesarean section, including two patients with intrauterine stillbirth at 31.6 and 24.9 weeks of gestation.

These patients received different anesthesia methods, including six patients with general anesthesia with tracheal intubation (TGA), 11 with epidural anesthesia, and four with spinal anesthesia combined with non-tracheal intubation of general anesthesia (NTGA). During cesarean section, 12 (57.1%) patients underwent ligation of the oviduct. At the moment of fetal retrieval, the SpO_2 of four patients was lower than 95%, and one patient had complicated hypotension. The mean perioperative bleeding of these patients was 344.17 ± 193.01 ml. The distribution of operation time, intraoperative vital sign monitoring, and medication for each patient are shown in **Figure 1** and **Supplementary Figures S1–S21**. The distribution of the operation time from starting anesthesia to surgery and from starting surgery to removing the fetus among the groups treated with various anesthesia methods was statistically significant ($P = 0.001$ and $P = 0.042$, respectively, **Figure 1**). Of the 21 patients undergoing cesarean section, 20 (95.2%) were transferred to the ICU immediately after surgery and received intensive monitoring of vital signs.

All PAH patients after pregnancy were reminded to receive adequate rest and nutrition. General medications were administered to 24 patients: Before delivery, antibiotics (8), diuretics (8), calcium channel blockers (CCB, 3) were used to control hypertension, and heparin (2). During delivery, antibiotics (18) and intrauterine injection of oxytocin (16), noradrenaline (9), dopamine (3), nitroglycerin (3), adrenaline (1), and dobutamine hydrochloride (1) were administered. After delivery, antibiotics (24), diuretics (10), noradrenaline (3), dopamine (2), heparin (2), CCB (2), angiotensin-converting enzyme inhibitor (1), and angiotensin receptor blocker (1) were administered.

TABLE 2 | Examination indicators and echocardiographic value before termination or delivery in PAH patients with pregnancy.

Patients	SpO_2, %	HB, g/L	PLT, $\times 10^9$/L	PT, s	APTT, s	Fbg, g/L	ALB, g/L	BNP, pg/ml	NT-proBNP, ng/L	Braden score	Barthel index	Echocardiographic value						
												PASP, mmHg	EF, %	LA diameter, mm	LV diameter, mm	RA diameter, mm	RV diameter, mm	PA diameter, mm
No. 1	69	190	58	11.1	38.3	2.48	25	125	–	13	90	139.1	60	26	50	43	22	31
No. 2	94	138	161	11.4	28	3.66	33	–	–	15	85	61	56	25	41	32	22	30
No. 3	99	126	212	10.9	28.0	5.0	30	–	863	18	30	103	69	27	39	45	28	34
No. 4	99	122	199	12.4	34.2	3.67	35	65.1	–	13	100	96.1	62	24	42	34	25	27
No. 4*	96	106	151	10.7	27.3	4.56	36	–	116	16	95	79	68	29	43	42	28	43
No. 5	98	111	198	11.2	24.5	3.27	38	379	< 1	17	80	71.5	67	42	42	30	27	–
No. 6	83	87	160	12	37.9	2.46	38	–	257	14	95	58	67	32	47	66	30	32
No. 7	65	125	194	12.4	34.5	3.67	28	–	4,249	15	90	93#	–	49	–	51	–	27
No. 8	91	141	138	10.2	29.1	4.36	43	420	–	18	90	123	59	35	42	42	24	25
No. 9	98	122	256	10.2	21.5	4.68	36	–	17	21	95	60.8	67	24	47	28	18	–
No. 10	99	106	234	11.7	28.7	4.82	36	–	1,360	15	90	76	46	44	70	42	26	20
No. 11	98	110	216	9.8	29.7	4.2	30	< 5	–	13	95	50	70	30	42	43	33	29
No. 12	97	122	224	11.9	24.3	4.35	33	–	206	13	100	60	65	34	37	60	39	35
No. 13	99	96	180	11.6	24.7	4.54	34	70	–	13	95	56	62	32	43	49	29	31
No. 14	99	152	128	13.8	40	2.9	40	–	64	13	100	61	72	24	41	30	17	25
No. 14*	82	153	102	10.9	30.7	4.33	38	13.7	–	14	100	66	63	24	44	33	20	32
No. 15	99	128	191	11.1	23.2	4.35	35	–	68	13	95	50.2	68	32	45	46	37	–
No. 16	91	180	130	10.9	30.3	3.97	39	17.5	–	13	100	81	63	31	49	44	24	37
No. 17	86	25	895	15	23.6	5.08	22	–	1,510	20	65	50.3	67	37	57	36	22	23
No. 18	90	88	180	17.1	44.4	2.87	24	882	2,540	14	90	127	58	45	60	46	26	45
No. 19	98	110	279	10.8	23.5	3.86	27	–	1,660	15	95	64.5	68	31	49	38	20	–
No. 20	97	86	267	12.2	28	5.22	37	–	>35,000	14	85	38	51	36	62	34	20	–
No. 21	97	125	290	10.4	27.7	4.19	36	–	14	13	100	35	59	31	45	43	31	28
No. 22	97	115	171	10.7	27.5	3.29	38	–	147	14	100	70.2	67	31	37	32	46	24

PAH, pulmonary arterial hypertension; SpO_2, percutaneous oxygen saturation; HB, hemoglobin; PLT, platelet; PT, coagulation time; APTT, activated partial thromboplastin time; Fbg, fibrinogen; ALB, albumin; BNP, B-type natriuretic peptide; NT-proBNP, N terminal pro B-type natriuretic peptide; PASP, pulmonary artery systolic pressure; EF, left ventricular ejection fraction; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle; PA, main pulmonary artery.

** The second pregnancy during the study period.*

 # Tricuspid valve pressure difference.

TABLE 3 | Intraoperative management of pregnancy termination in PAH patients with pregnancy.

Patients	GW of delivery, wk	Delivery mode	Anesthesia	PFDW	Uterine contraction	Oxytocin, IU	PB, ml	Amniotic fluid, ml	Ligation of oviduct	Length of operation, min	The moment of fetus retrieval				
											T, °C	RR, bpm	HR, bpm	BP, mmHg	SpO_2, %
No. 1	37	Cesarean section	TGA	Natural	Strong	20	500	400	No	55	36.5	12	86	162/88	81
No. 2	34.4	Cesarean section	EA	Natural	Strong	5	500	350	Yes	120	36.5	23	98	104/57	97
No. 3	37	Cesarean section	SA + NTGA	Natural	Strong	10	300	350	Yes	115	36.5	40	94	105/61	100
No. 4	14.6	Medical induction	–	Uterine curettage	–	–	110	–	–	–	–	–	–	–	–
No. 4*	35.3	Cesarean section	EA	Natural	Strong	0	200	500	Yes	125	35.5	16	77	120/58	99
No. 5	21.1	Medical induction	–	Natural	–	–	300	–	–	–	–	–	–	–	–
No. 6	32.3	Cesarean section	EA	Manual	Strong	15	500	500	Yes	130	36.4	20	90	141/70	100
No. 7	31.3	Cesarean section	TGA	Manual	Weak	0	600	1,000	Yes	81	36	12	90	118/73	93
No. 8	35	Cesarean section	TGA	Natural	Weak	0	500	600	Yes	47	36.5	12	73	79/48	94
No. 9	37	Cesarean section	EA	Natural	Weak	0	300	600	Yes	85	36.3	14	82	126/67	100
No. 10	37.4	Cesarean section	EA	Natural	Poor	0	100	100	No	70	36.5	28	109	112/71	99
No. 11	36.9	Cesarean section	EA	Natural	Strong	10	200	400	Yes	70	36	21	102	118/75	100
No. 12	37.9	Cesarean section	EA	Natural	Strong	5	300	700	Yes	110	36.3	15	104	146/85	100
No. 13	36.3	Cesarean section	EA	Natural	Strong	10	200	500	No	70	37.2	17	119	102/61	100
No. 14	11.3	Medical induction	–	Uterine curettage	–	–	50	–	–	–	–	–	–	–	–
No. 14*	33.9	Cesarean section	EA	Natural	Weak	5	300	500	Yes	80	36	26	83	165/81	92
No. 15	36.3	Cesarean section	EA	Natural	Strong	10	500	500	Yes	220	36.5	25	91	135/71	100
No. 16	34	Cesarean section	TGA	Manual	Strong	10	400	500	Yes	64	36.5	12	70	125/72	99
No. 17	31.6	Cesarean section	TGA	Natural	Strong	20	200	500	No	40	36.8	13	80	113/68	100

(Continued)

TABLE 3 | Continued

Patients	GW of delivery, wk	Delivery mode	Anesthesia	PFDW	Uterine contraction	Oxytocin, IU	PB, ml	Amniotic fluid, ml	Ligation of oviduct	Length of operation, min	The moment of fetus retrieval				
											T, °C	RR, bpm	HR, bpm	BP, mmHg	SpO_2, %
No. 18	32.7	Cesarean section	EA	Natural	Poor	20	750	600	No	70	36.6	21	133	163/95	100
No. 19	24.9	Cesarean section	SA + NTGA	Natural	Strong	20	750	300	No	125	36.5	24	76	153/76	100
No. 20	33.9	Cesarean section	SA + NTGA	Natural	Strong	10	200	400	No	90	37.3	27	108	161/91	99
No. 21	37.4	Cesarean section	TGA	Natural	Weak	20	300	1,200	No	38	36.5	12	115	105/60	99
No. 22	37.4	Cesarean section	EA	Natural	Weak	5	200	600	No	91	35.7	22	90	147/77	100

PAH, pulmonary arterial hypertension; GW, gestational week; wk, week; TGA, general anesthesia with tracheal intubation; SA + NTGA, spinal anesthesia combined with non-tracheal intubation of general anesthesia; EA, epidural anesthesia; PFDW, placenta and fetal membrane delivery way; IU, international unit; PB, peroperative bleeding; T, temperature; RR, respiratory rate; bpm, beats per minute; HR, heart rate; BP, blood pressure; SpO_2, percutaneous oxygen saturation.

*The second pregnancy during the study period.

Pulmonary Vasodilators

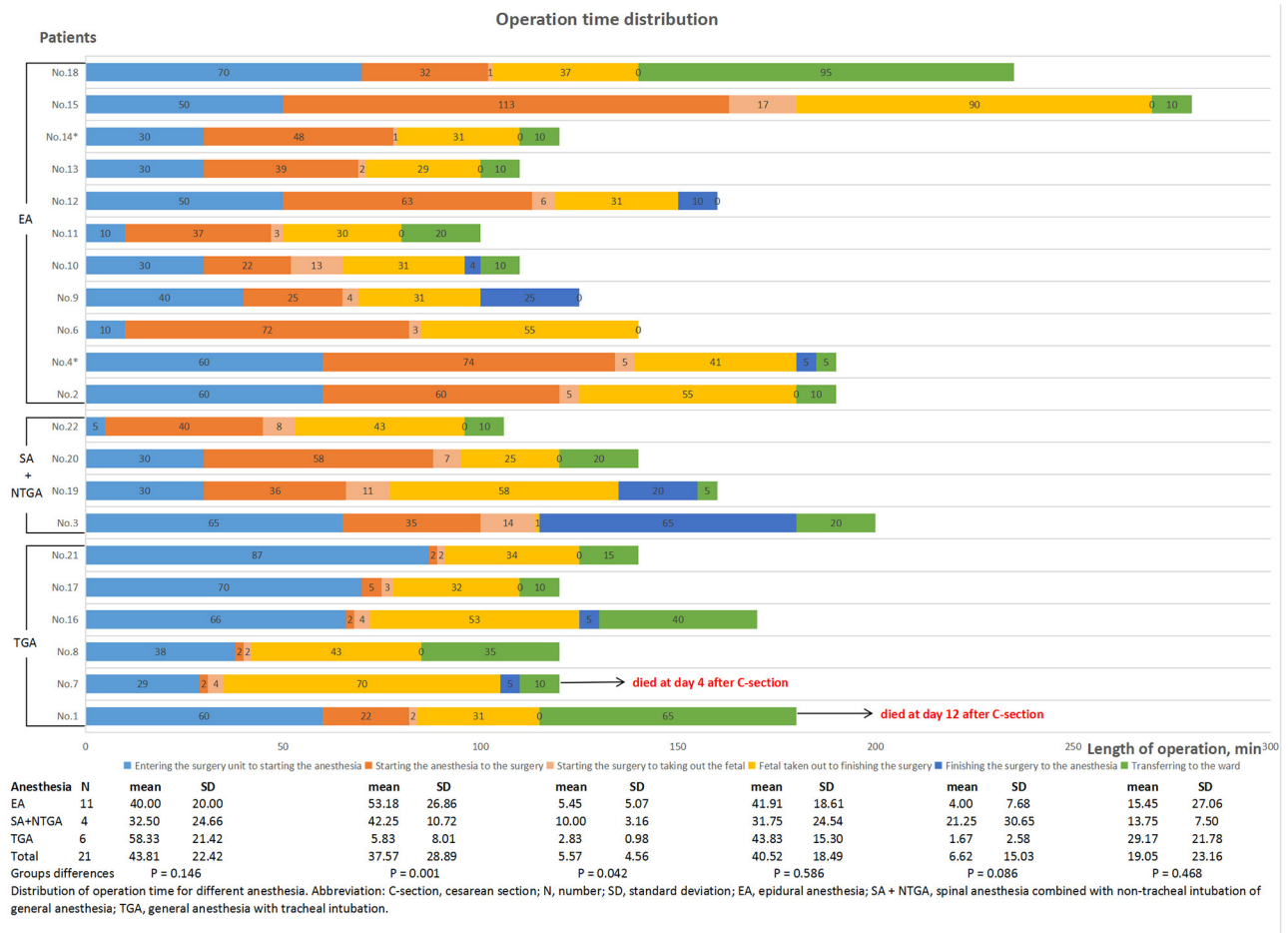
Overall, eight patients received pulmonary vasodilators throughout the perinatal period, while three did not receive any PAH-targeted therapies (**Tables 1**, **4**, and **Supplementary Figures S1–S21**). There were 21 (87.5%) pregnancies receiving PAH-targeted therapy: 17 (70.8%) of them received pulmonary vasodilators before operation, of which seven received treprostinil alone, one received sildenafil alone, eight received treprostinil combined with tadalafil, and one received treprostinil combined with sildenafil; 10 (41.7%) received treprostinil intraoperatively; and 19 (79.2%) received post-operatively, of which seven pregnancies received monotherapy (treprostinil or sildenafil) and 12 were treated with a combination of pulmonary vasodilators.

Maternal Outcomes

No deaths occurred during pregnancy. The maternal survival rate of PAH patients who became pregnant in the present study was 91.7%. Two (8.3%) patients died during the early post-partum period (4 and 12 days after delivery, individually). Both of the deceased patients had PAH-CHD, severe PAH, right heart failure, and multiple pregnancies. Their SpO_2 with oxygen was <70% under room air before surgery and <95% at the moment of fetal retrieval, and they both received cesarean section under TGA. One patient had an atrial septal defect (ASD), and the other patient had corrected transposition of great arteries combined with a single ventricle. Other patients discharged from the hospital remained alive to the point of presentation of this study. The follow-up period for discharge ranged from 1.5 months to 4.5 years (median 2 years).

Fifteen (62.5%) pregnancies were complicated with SAE, and their RV diameter was larger than those without SAE (30.56 ± 7.57 mm vs. 24.21 ± 5.67 mm, $P < 0.032$, **Supplementary Table S5**). Eleven (45.8%) pregnancies were complicated HF, six (25%) suffered RF, and 10 (41.7%) suffered post-operative infections. Compared with the subgroups without adverse events, deceased patients had a lower admitted SpO_2, lower albumin (ALB), higher PASP, and higher BP ($P < 0.05$, **Table 4** and **Supplementary Table S5**), patients complicated HF showed a longer activated partial thromboplastin time (APTT) and lower fibrinogen (Fbg), patients complicated with RF showed a lower SpO_2, longer APTT, lower Barthel index, higher PASP, and higher BP. Patients complicated with post-operative infections had a lower SpO_2, longer coagulation time, longer APTT, and higher PASP. TGA was significantly related to death and infection (**Supplementary Table S5**).

The vital signs of 21 patients undergoing cesarean section were closely monitored during the operation (**Supplementary Figures S1–S21**). Thirteen (61.9%) pregnancies had SAE, including two pregnancies (9.5%) that died, nine (42.9%) complicated with HF, six (28.6%) that suffered RF, and nine (42.9%) that suffered post-operative infections (**Table 4**). Compared with the subgroups without corresponding adverse events, lower SpO_2 at the time of fetal removal was related to death and RF ($P = 0.00$ and 0.049, respectively, **Supplementary Table S6**), and higher systolic and diastolic BP were related to HF ($P = 0.032$ and 0.018, respectively,



Anesthesia	N	mean	SD	mean	SD	mean	SD	mean	SD	mean	SD	mean	SD
EA	11	40.00	20.00	53.18	26.86	5.45	5.07	41.91	18.61	4.00	7.68	15.45	27.06
SA+NTGA	4	32.50	24.66	42.25	10.72	10.00	3.16	31.75	24.54	21.25	30.65	13.75	7.50
TGA	6	58.33	21.42	5.83	8.01	2.83	0.98	43.83	15.30	1.67	2.58	29.17	21.78
Total	21	43.81	22.42	37.57	28.89	5.57	4.56	40.52	18.49	6.62	15.03	19.05	23.16
Groups differences		P = 0.146		P = 0.001		P = 0.042		P = 0.586		P = 0.086		P = 0.468	

Distribution of operation time for different anesthesia. Abbreviation: C-section, cesarean section; N, number; SD, standard deviation; EA, epidural anesthesia; SA + NTGA, spinal anesthesia combined with non-tracheal intubation of general anesthesia; TGA, general anesthesia with tracheal intubation.

FIGURE 1 | Distribution of operation time for different anesthesia conditions.

Supplementary Table S6). Other vital signs were not significantly different in the subgroups with or without adverse events.

The average hospital stay for 24 pregnancies was 16 ± 8.0 days, of which the ICU stay period was 3.4 ± 3.9 days (**Table 4**). Compared with childbirth without PAH, the hospital stay of PAH women was significantly longer (13). The average expenditure during hospitalization before reimbursement was ¥ 38645.6 ± 33660.5, which was 10 times the expanses without PAH (¥ 3824.50) (14). The medical insurance type in 14 (58.3%) pregnancies was urban resident basic medical insurance (URBMI, reimbursement ratio 20%), six (25%) were urban employee basic medical insurance (UEBMI, reimbursement ratio 75%), one (4.2%) was a new rural cooperative medical scheme (NRCMS, reimbursement ratio 20%), and three (12.5%) had not purchased any medical insurance were paying for medical care at their own expense.

Fetal/Neonatal Outcomes

Eighteen (85.7%) newborns who survived after the operation remained alive (**Table 5**). Eight (44.4%) newborns were transferred to the neonatology department immediately after birth, and the families of the other 10 (55.6%) newborns refused section transfer. In the 21 cesarean sections, 14 (66.7%) pregnancies were prematurely delivered.

DISCUSSION

This study observed a high survival rate in parturients and neonates with PAH pregnancy, which may be related to intensive management of MDT and pulmonary vasodilator therapy during the perinatal period. However, the incidence of maternal complications was still high, causing long hospital stays and high expenditures. PAH patients had high risks of poor outcomes during the perinatal period, especially in the early post-partum period. The monitoring time by MDT for PAH patients with pregnancy started slightly late in this center. The present study observed a strong association between SAE and low SpO_2 and ALB, high PASP, increased right heart diameter and BP, and severe coagulopathy.

Pulmonary Vasodilator Therapy

With the development of PAH-targeted therapies such as prostacyclins, phosphodiesterase inhibitors 5 (PDE5i), and

TABLE 4 | Post-operative management and outcome at discharge of PAH patients with pregnancy.

Patients	Maternal outcome at hospital discharge				ICU stay, d	Hospital stay, d	Hospitalization expenditure, million	Proportion of drug expenditure, %	Medical insurance	PVs therapy after delivery		Present status	Time after discharge
	Survival status	HF	RF	Infection						Medicine	Dose		
No. 1	Deceased	Yes	Yes	Yes	6	20	8.18	13.4	URBMI	Treprostinil	20 ng/kg/min	–	–
No. 2	Alive	Yes	No	No	4	32	8.82	5.85	URBMI	Treprostinil & Sildenafil	20 ng/kg/min 25 mg tid	Alive	4.5 y
No. 3	Alive	No	Yes	Yes	13	35	16.67	19.64	URBMI	Treprostinil & Tadalafil & Ambrisentan	20 ng/kg/min 10 mg qd 2.5 mg qd	Alive	4 y
No. 4	Alive	No	No	No	0	15	2.66	0.82	UEBMI	Treprostinil & Tadalafil	20 ng/kg/min 10 mg qd	Alive	4 y
No. 4*	Alive	No	No	No	1	13	2.51	5.1	UEBMI	Treprostinil & Tadalafil	20 ng/kg/min 20 mg qd	Alive	2 y
No. 5	Alive	Yes	No	No	2	16	1.59	8.56	URBMI	Treprostinil & Sildenafil & Bosentan	20 ng/kg/min 25 mg tid 62.5 mg tid	Alive	3.5 y
No. 6	Alive	Yes	Yes	Yes	0	24	5.27	16.13	UEBMI	Treprostinil & Tadalafil	20 ng/kg/min 20 mg qd	Alive	4 y
No. 7	Deceased	Yes	Yes	Yes	13	18	4.93	19.11	URBMI	Treprostinil	20 ng/kg/min	–	–
No. 8	Alive	No	Yes	Yes	11	15	4.14	12.41	URBMI	Treprostinil	20 ng/kg/min	Alive	2 y
No. 9	Alive	No	No	Yes	1	10	2.04	9.44	Self–supporting	Treprostinil	20 ng/kg/min	Alive	2 y
No. 10	Alive	No	No	No	6	16	2.98	15.63	Self–supporting	–	–	Alive	2 y
No. 11	Alive	No	No	No	1	15	2.34	9.83	Self–supporting	Treprostinil & Tadalafil	20 ng/kg/min 10 mg qd	Alive	2 y
No. 12	Alive	Yes	No	No	4	16	2.50	9.07	URBMI	Treprostinil & Sildenafil	20 ng/kg/min 25 mg tid	Alive	14 m

(Continued)

TABLE 4 | Continued

Patients	Maternal outcome at hospital discharge				ICU stay, d	Hospital stay, d	Hospitalization expenditure, million	Proportion of drug expenditure, %	Medical insurance	PVs therapy after delivery		Present status	Time after discharge
	Survival status	HF	RF	Infection						Medicine	Dose		
No. 13	Alive	No	No	No	3	10	2.30	19.9	URBMI	Treprostinil & Bosentan	20 ng/kg/min 62.5 mg bid	Alive	14 m
No. 14	Alive	Yes	No	Yes	0	8	0.73	8.82	Self–supporting	–	–	Alive	5 y
No. 14*	Alive	No	No	No	1	32	2.79	5.41	URBMI	Treprostinil & Tadalafil & Macitentan & Beraprost Sodium	20 ng/kg/min 10 mg qd 10 mg qd 40 ug tid	Alive	13.5 m
No. 15	Alive	No	No	No	1	7	1.64	10.18	UEBMI	Treprostinil	20 ng/kg/min	Alive	13 m
No. 16	Alive	Yes	No	Yes	1	18	2.50	8.45	NRCMS	Treprostinil & Tadalafil	20 ng/kg/min 10 mg qd	Alive	18.5 m
No. 17	Alive	No	No	Yes	3	12	4.74	23.87	URBMI	Treprostinil	20 ng/kg/min	Alive	5.5 m
No. 18	Alive	Yes	Yes	Yes	4	17	4.62	18.41	URBMI	Sildenafil	20 mg tid	Alive	16.5 m
No. 19	Alive	Yes	No	No	3	11	2.49	7.39	UEBMI	–	–	Alive	4.5 m
No. 20	Alive	Yes	No	No	1	13	2.87	10.03	URBMI	–	–	Alive	5.5 m
No. 21	Alive	No	No	No	0	6	1.85	15.56	UEBMI	–	–	Alive	17.5 m
No. 22	Alive	No	No	No	2	5	1.59	6.5	URBMI	Treprostinil	20 ng/kg/min	Alive	1.5 m

PAH, pulmonary arterial hypertension; HF, heart failure; RF, respiratory failure; ICU, intensive care unit; URBMI, urban residents basic medical insurance; UEBMI, urban employee basic medical insurance; NRCMS, new rural cooperative medical scheme; PVs, pulmonary vasodilators; qd, once daily; bid, twice daily; tid, three times daily; y, year; m, month.

**The second pregnancy during the study period.*

TABLE 5 | Status of the fetus and the newborn after delivery.

Patients	Fetal status		Neonate				Apgar score			Transfer to neonatology
	IUGR	FGR	Survival status	Birth weight, g	Gender	Premature	1 min	5 min	10 min	
No. 1	Yes	Yes	Alive	1,190	Male	Full-term	5	5	6	No
No. 2	No	No	Alive	UN	Male	Pre-term	9	10	10	No
No. 3	Yes	No	Alive	UN	Female	Full-term	9	9	10	Yes
No. 4*	No	No	Alive	UN	Male	Pre-term	9	10	10	Yes
No. 6	No	No	Alive	1,800	Male	Pre-term	8	9	9	Yes
No. 7	Yes	Yes	Deceased**	UN	Female	Pre-term	5	8	8	No**
No. 8	Yes	No	Alive	UN	Female	Pre-term	6	8	9	No
No. 9	No	No	Alive	UN	Female	Full-term	10	10	10	Yes
No. 10	No	No	Alive	2,850	Female	Full-term	9	10	10	No
No. 11	No	No	Alive	2,860	Female	Pre-term	9	10	10	No
No. 12	No	No	Alive	3,605	Male	Full-term	9	10	10	No
No. 13	No	No	Alive	2,525	Female	Pre-term	10	10	10	No
No. 14*	Yes	No	Alive	UN	Male	Pre-term	9	10	10	Yes
No. 15	No	No	Alive	2,755	Male	Pre-term	10	10	10	No
No. 16	Yes	No	Alive	1,725	Male	Pre-term	9	10	10	Yes
No. 17	Yes	Yes	Stillborn***	1,000	Female	Pre-term	UN	UN	UN	No***
No. 18	No	No	Alive	UN	Male	Pre-term	10	10	10	Yes
No. 19	No	No	Stillborn***	UN	Male	Pre-term	UN	UN	UN	No***
No. 20	Yes	No	Alive	1,885	Female	Pre-term	9	9	10	Yes
No. 21	No	No	Alive	2,600	Male	Full-term	5	7	8	Yes
No. 22	Yes	No	Alive	2,465	Male	Full-term	9	10	10	No

The second pregnancy during the study period.

**The newborn died on the second day after birth.*

***The two fetuses were dead before the cesarean section.*

IUGR, fetal in utero distress; FGR, fetal growth restriction; UN, unknown.

endothelin receptor antagonists (ERAs), PAH has been well-controlled (1). In this study, most patients used single (prostacyclins or PDE5is) or combined (prostacyclins combined with PDE5is) pulmonary vasodilator therapy during the perinatal period, and the maternal survival rate reached 91.7%. Perinatal PAH targeted therapy was beneficial to the maternal outcomes of PAH (1, 15). However, there is a lack of clinical evidence for the recommended dose of pulmonary vasodilators for PAH patients during pregnancy. In the present study, treprostinil was initiated at 1.25 ng/kg/min and titrated by 2.5 ng/kg/min every 6 h to a final dose of 20 ng/kg/min during the pre- and post-operative period (16) which was lower than the effective dose (40–60 ng/kg/min) routinely used for non-pregnant PAH patients (17, 18). Mainly due to it not being reimbursed in China and high cost (¥ 9,800/20 mg), it was administered at 5 ng/kg/min to 50 ng/kg/min during the operative period. Treprostinil, tadanafil, and sildenafil are not included in medical insurance in China. These drugs were purchased outside the hospital, and this cost was not included in the hospitalization expenses. Studies have shown that ERAs are teratogenic (3) and should be suspended during pregnancy and used in combination after delivery. Due to the physiological changes and complications that occur during pregnancy, it is vital to monitor patients carefully and make dose adjustments as necessary throughout pregnancy and delivery (7).

Clinical Outcomes

Previous systematic overviews and selected case series have reported a high mortality rate (12–56%) in PAH women pregnant (5, 19). However, little is known about the risk factors related to the adverse events of perinatal PAH. In the present study, the incidence of SAE was high (62.5%), and two patients with congenital heart disease died in the early perinatal period. Both of them were in serious hypoxemia (mean SpO_2 67% under room air) when admitted to the hospital and did not receive pulmonary targeted vasodilator treatment before pregnancy. The two deceased patients received oxygen inhalation and targeted PAH therapy after admission, but the level of SpO_2 was still <95% with 5 L/min oxygen supplementation at the moment of fetal retrieval. Furthermore, this study found that patients with low admitted SpO_2 had more intraoperative blood loss, which may be related to the weak contraction of the uterine muscles under hypoxia (20). Long-term refractory hypoxia might be related to an increased risk of death (21). Admitted SpO_2, low ALB, elevated PASP and BP were significantly related to death in this study. PAH patients with abnormalities above during pregnancy should be strongly recommended to prohibit or terminate pregnancy.

All patients undergoing cesarean section were closely monitored for intraoperative vital signs. This study found that patients with adverse events presented with lower SpO_2 and

higher BP at the moment of fetal retrieval. PAH patients with the above abnormalities during surgery should be further vigilant about poor outcomes after delivery. These potential risk factors need to be confirmed in prospective studies in the future.

Pregnant women are accompanied by physiological changes with increased cardiac output. However, the diseased pulmonary vascular system of PAH patients cannot withstand increased cardiac output, resulting in strain and dilation of the right ventricle and ultimately decompensation (3, 12). This study found that severely increased PASP was prone to death, which was consistent with the risk factors proposed in the current guidelines (1, 7). The present study also showed that a higher PASP was significantly related to the occurrence of RF and infection. Eclampsia is one of the dangerous complications of pregnant women (22). There were four patients with hypertension at admission, and elevated BP was associated with death and/or HF. BP at the moment of fetal retrieval in eight patients was higher than the normal level, except one was lower. PAH patients during pregnancy might be more sensitive to BP fluctuations. Therefore, more close monitoring of BP in patients with PAH during pregnancy is necessary. Pregnant women are at risk of hypercoagulability, especially fatal pulmonary embolism (23). Antithrombosis is traditionally used in pregnancies during the perinatal period. More detailed studies on the dosage and time of antithrombotic treatment are needed.

MDT Management

Complete MDT is essential for the comprehensive management of PAH patients during pregnancy (**Figure 2**) (24). All patients in the present study received tailor-made MDT management. Unfortunately, the start of monitoring time by the MDT team for pregnant women was relatively late in this center, which was detrimental to risk control during pregnancy. Because the maternal mortality rate remains high, patients with PAH are recommended to take contraception (7). Early maternity examinations for pregnant women are essential because PAH is more common in women, and the initial clinical manifestations may occur during pregnancy (7, 10, 11). For pregnant women, echocardiography is utilized to screen for PAH, which is non-invasive, repeatable, and easy to perform (7). With patient consent, it is recommended to perform invasive RHC at an experienced PAH center, and genetic testing can be performed if necessary (7). In this study, the SAE incidence of parturients with PAH was as high as 62.5%. Once PAH with pregnancy is diagnosed, patients need to be informed of the high risk of SAE during pregnancy and after delivery, and medical termination should be recommended. Patients who require continued pregnancy need to receive periodic follow-ups at PAH specialists and obstetricians, monitor PASP, right ventricular function, oxygen saturation, BNP/NT-proBNP, and fetal monitoring (7, 10, 11). During the follow-up, oxygen inhalation, adequate rest, and enhanced nutrition are required. Anti-PAH and anti-heart failure treatments are recommended to being actively given at least 3 months before delivery. Risk assessment should be performed monthly during pregnancy. Once the condition is unstable, emergency admission and prompt termination of the pregnancy are necessary.

No spontaneous abortion occurred in this study. Three patients chose medical induction at 11.3, 14.6, and 21.1 weeks. Two patients had intrauterine stillbirths during pregnancy, and cesarean section was performed at 31.6 and 24.9 weeks. Monitoring of pregnant women and fetuses during pregnancy is essential. The patients included in this study were all diagnosed with PAH and pregnancy when they were admitted to the hospital. PAH patients who aborted outside the hospital were not included. The abortion rate of women with PAH was not investigated in the present study. Complete MDT management is required during the third trimester and the entire perinatal period. Pregnant women with PAH should be hospitalized promptly when severe hypoxemia, deteriorated heart failure, coagulation dysfunction, hypertension, and fetal abnormalities occur. Communication should be strengthened with pregnant women and routine follow-up to help them fully understand their condition and improve the compliance of treatments. Pregnant women need to receive PAH-targeted therapy, anti-heart failure, anti-thrombosis, and anti-infection and to promote fetal lung maturity during the perinatal period. During normal pregnancy, blood flow and cardiac output will increase, reaching their peaks at approximately 32 and 24 weeks of gestation, respectively (25). Compared with normal pregnant women, patients with PAH-CHD are intolerant to this physiological change during pregnancy. The increase in PVR in pregnant women with PAH further aggravates PAH, overloads the right ventricle, and ultimately seriously affects right ventricular function (3). In the present study, the premature delivery rate of PAH patients who persisted in continuing pregnancy was high (66.7%). After discussion through MDT, they all chose to perform cesarean section with a mean gestational term of 32.37 weeks, and all of the preterm births were determined by MDT through discussion of the status of the pregnant woman and the fetus. The detailed delivery plan should be developed through MDT discussion, including delivery timing, delivery method, anesthesia method, and oviduct ligation; and communication with the patient to give a full sense of safety. Intraoperative monitoring of the patient's vital signs is important, and it is necessary to continue anti-PAH, maintain circulation, and anti-infective treatments (3). PAH patients are prone to hypoxemia (1), and this study found that it directly affects intraoperative bleeding. Intravenous administration of oxytocin may incr ease the burden on the heart of patients (26, 27), but the bleeding volume of 76.2% of patients in this study was well-controlled by injection of oxytocin through the uterine wall. However, there is currently no study on the dose of oxytocin related to uterine wall injection, and it needs to be administered reasonably according to the uterine contraction and the patient's condition. The highest-risk period for the patients is the puerperium and the early post-partum period (7). It is necessary to transfer to the ICU after delivery. PAH-targeted therapy, anti-heart failure, anti-thrombosis, and anti-infection therapies are recommended to be maintained until the patient is discharged. It is recommended that mothers with PAH avoid breastfeeding after delivery because pulmonary vasodilators may be excreted through breast milk (28). Breastfeeding can also increase maternal fatigue, which is detrimental to the post-partum recovery of PAH patients.

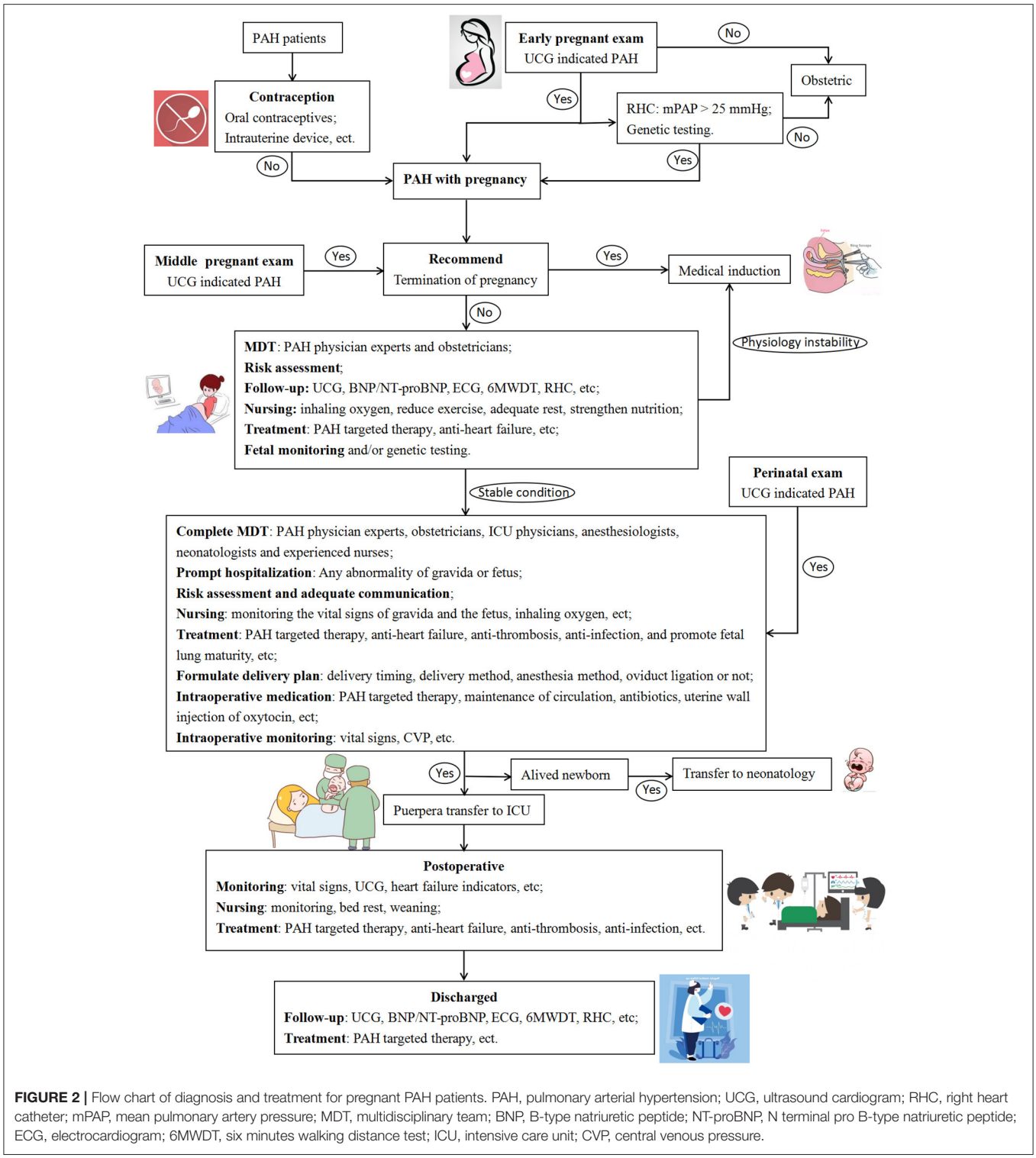


FIGURE 2 | Flow chart of diagnosis and treatment for pregnant PAH patients. PAH, pulmonary arterial hypertension; UCG, ultrasound cardiogram; RHC, right heart catheter; mPAP, mean pulmonary artery pressure; MDT, multidisciplinary team; BNP, B-type natriuretic peptide; NT-proBNP, N terminal pro B-type natriuretic peptide; ECG, electrocardiogram; 6MWDT, six minutes walking distance test; ICU, intensive care unit; CVP, central venous pressure.

To improve the survival rate, it is recommended that neonates be transferred to neonatology after birth. Late hospitalization increases the risk of adverse events. Therefore, it is critical for patients with PAH in the middle and late stages of pregnancy to be surveillant and treated with the experienced MDT team.

Limitations

The present study was a retrospective single-center trial and reported a relatively small number of patients, so recall bias or reporting bias are unlikely. Due to the small sample size, this study was unable to perform quantitative analysis and identify risk factors. Strengthening of vigilance and management of PAH

patients with pregnancy are needed. The patients included in this study were mostly based on UCG and lacked hemodynamic parameters. Due to the small sample size, the failure to conduct a multifactor analysis of all indicators may cause statistical bias in the results. However, not only the baseline characteristics but also the vital signs during and after cesarean section in each patient were collected to investigate the potential risk factors for SAE.

CONCLUSION

The survival rate of parturients and neonates with PAH has been improved due to MDT management and pulmonary vasodilator therapy during the perinatal period. However, PAH during pregnancy remains a substantial risk and commonly leads to SAE, especially in the early post-partum period. SpO_2, ALB, PASP, BP, and coagulation function should be carefully monitored in pregnant PAH patients. Prospective and multicenter studies with large sample sizes in women with PAH are required to determine the pregnancy-related risk factors, supportive care strategies and advanced PAH therapy.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding authors.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the First Affiliated Hospital of Chongqing Medical University. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

TS and PF were responsible for the study screening, data extraction, and writing the manuscript. XL contributed to data analysis. LW, HC, and YC were responsible for checking and reviewing the final manuscript. All authors have read and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2021.795765/full#supplementary-material

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BRIEF RESEARCH REPORT
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Center-To-Periphery Arterial Stiffness Gradient Is Attenuated and/or Reversed in Pregnancy-Associated Hypertension

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Background: Non-pregnant (NP) women have a progressive increase in arterial stiffness from central-to-peripheral arteries ["stiffness gradient" (SG)], which is of physiologic importance since excessive pulsatility is filtered by the creation of wave reflections. If the aorta gets stiff with minimal or no change in the periphery, the SG is dissipated transmitting pressure disturbances to the microcirculation. It remains unknown the status of the SG in both women with healthy pregnancies (HP) and complicated by pregnancy-associated hypertension (PAH).

Objective: To determine whether HP and PAH are associated with changes in SG. Secondarily, we aim at identifying potential differences between the subgroups of PAH (pre-eclampsia and gestational hypertension).

Methods: HP ($n = 10$), PAH ($n = 16$), and healthy NP women ($n = 401$, to be matched for age, and cardiovascular risk with the pregnant women) were included. Carotid-to-femoral (cfPWV) and carotid-to-radial pulse wave velocity (crPWV), common carotid artery (CCA) and brachial artery (BA) diameters and elastic modulus (EM), and regional (cfPWV/crPWV or "PWV ratio") and local (CCA EM/BA EM or "EM ratio") SG were quantified.

Results: HP showed no changes in PWV ratio compared with NP, in the presence of significantly lower cfPWV and crPWV. HP exhibited higher arterial diameters and lower CCA EM/BA EM compared to NP, without differences with PAH. PAH was associated with a significant increase in the PWV ratio that exceeded the levels of both NP and HP, explained by a lower (although significant) reduction of cfPWV with respect to that observed in HP with respect to NP, and a higher reduction in crPWV with respect to that observed between HP and NP. The blunted reduction in cfPWV observed in PAH coincided with an increase in the CCA EM.

Conclusions: Compared with NP, HP was associated with unchanged PWV ratio but with a reduction in CCA EM/BA EM, in the setting of a generalized drop in arterial stiffness. Compared with NP and HP, PAH was associated with an "exaggerated rise" in the PWV

ratio without changes in CCA EM/BA EM, in the setting of a blunt reduction in cfPWV but exaggerated crPWV drop. The SG attenuation/reversal in PAH was mainly driven by pre-eclampsia.

Keywords: arterial stiffness, carotids, gestational hypertension, pregnancy, pre-eclampsia

INTRODUCTION

Pre-eclampsia (PE) and gestational hypertension (GH), collectively denominated as pregnancy-associated hypertension (PAH), complicate 3–8% of all pregnancies with serious short- and long-term maternal and neonatal consequences (1–3). While some evidence suggests that GH and PE may represent different disorders, several investigations support that GH could in fact be a milder manifestation of PE, and that these conditions are a continuous spectrum of the same pregnancy-induced syndrome (1, 3). Yet, the pathophysiology of PAH remains to be fully elucidated. The most accepted theory proposes that an impaired placentation (i.e., shallow invasion of trophoblast of the spiral arteries) results in a dramatic rise in the resistance of the uterine-placental vasculature, which leads to a rapid development of a disproportionate rise in blood pressure (BP), inappropriate inflammatory response, generalized endothelial dysfunction, and multi-organ damage ("placental origin hypothesis") (4). However, this hypothesis was recently questioned, since placental histopathology lesions thought to be characteristic of this condition are neither sensitive nor specific markers for the disorder (5, 6).

Recent evidence has revealed that PAH may develop in those women that are not able to develop an optimal cardiovascular adaptation to the naturally occurring hemodynamic loads of pregnancy ("cardiovascular origin hypothesis") (5, 7). In this hemodynamic context (e.g., increased BP and arterial stiffness), excessive pulsatility in the central arteries may be preferentially transmitted to the placental microvasculature ("secondary placental dysfunction"), as well as to other vulnerable circulations. Recently, our group reviewed the available evidence and concluded that both theories ("placental and cardiovascular origin") may be complementary and, a combined theory may be reasonable for most women (5). However, although the analysis of the current literature supports that PAH would be associated with several arterial abnormalities that would prevent an optimal reduction of the peripheral propagation of the pressure pulsatility, being this a potential link between both theories, many of these pathophysiologic clues remain to be confirmed through studies that simultaneously assess different regions of the vascular system.

Since healthy pregnancy (HP) is characterized by a pronounced increase in stroke volume (SV) and cardiac output (CO) to meet metabolic requirements, low aortic stiffness plays a key role in preventing large increases in pulse pressure (PP) and systolic BP (SBP) during pregnancy (8). In normal conditions, forward pressure waves generated intermittently by the left ventricle (LV) and re-reflections of backward propagating waves at the ventricular-aorta interface, travel throughout the arterial system and collide with reflection sites located in the arterial tree and reflect to the center as backward or retrograde pressure waves (9, 10). Pressure wave reflections can originate in multiple sites, such as arterial narrowing and bifurcations, but particularly, where the arterial stiffness (AS) of one region changes to another ["stiffness gradient" (SG)] (8–10). In healthy non-pregnant (NP) populations, there is a progressive increase in the AS from the aorta to the peripheral arteries, which is of physiologic importance since creates partial wave reflections reducing the energy carried peripherally by the forward wave to the microcirculation (11, 12). If the aorta becomes stiff with minimal or no changes in the peripheral vessels, the SG is dissipated (or reversed) increasing the risk of transmitting high pulsatile energy preferentially to low-resistance vascular beds (13–15). Aortic stiffness was found consistently elevated in PAH compared to HP in several cross-sectional (16–19) and prospective studies (20, 21), whereas changes in peripheral vascular stiffness have been a matter of debate. Yet, it remains unknown the status of the SG in women with PAH, which would have a paramount role in decreasing distal pulsatility and protecting the microcirculatory beds.

Since the speed of pressure wave propagation in a specific arterial region is proportional to its stiffness, the measurement of pulse wave velocity (PWV) has been conveniently used as a surrogate of regional AS (**Figure 1**) (8–10). Moreover, the PWV ratio [i.e., carotid-to-femoral PWV (cfPWV)/carotid-to-radial PWV (crPWV)], the relationship between the stiffness of central elastic and muscular peripheral arterial pathways, has been used as a trustworthy tool to evaluate the SG, being independently associated with increased mortality in kidney disease, stroke, and hypertension (11–13, 22). Alternatively, the SG could be also quantified by using local measures of AS [e.g., elastic modulus (EM)]. In theory, local indices of AS could be more sensitive to detect incipient (mild) vascular changes compared with regional indices (i.e., PWV ratio). Moreover, since PWV and EM are inversely determined by increases in arterial diameters (the larger the diastolic diameter the lower the PWV, but the higher EM) (**Figure 1**), which characteristically occur during pregnancy,

Abbreviations: aoBP, Central aortic blood pressure; AS, Arterial stiffness; BA, Brachial artery; baBP, Brachial artery blood pressure; baDBP, Brachial artery diastolic blood pressure; baSBP, Brachial artery systolic blood pressure; BP, Blood pressure; CCA, Common carotid artery; cfPWV, Carotid-to-femoral pulse wave velocity; CO, Cardiac output; CRFs, Cardiovascular risk factors; crPWV, Carotid-to-radial pulse wave velocity; DD, End-diastolic arterial diameter; EM, Pressure-strain elastic modulus; GH, Gestational hypertension; HP, Healthy pregnancy; HR, Heart rate; IMT, Intima-media thickness; LL, Lower limit; MBP, Mean blood pressure; MV, Mean value; PAH, Pregnancy-associated hypertension; PE, Preeclampsia; PP, Pulse pressure; PWA, Pulse wave analysis; PWV, Pulse wave velocity; SBP, Systolic Blood Pressure; SD, Standard deviation; SG, Stiffness gradient; SV, Stroke volume; SysD, Peak systolic arterial diameter; UL, Upper limit.

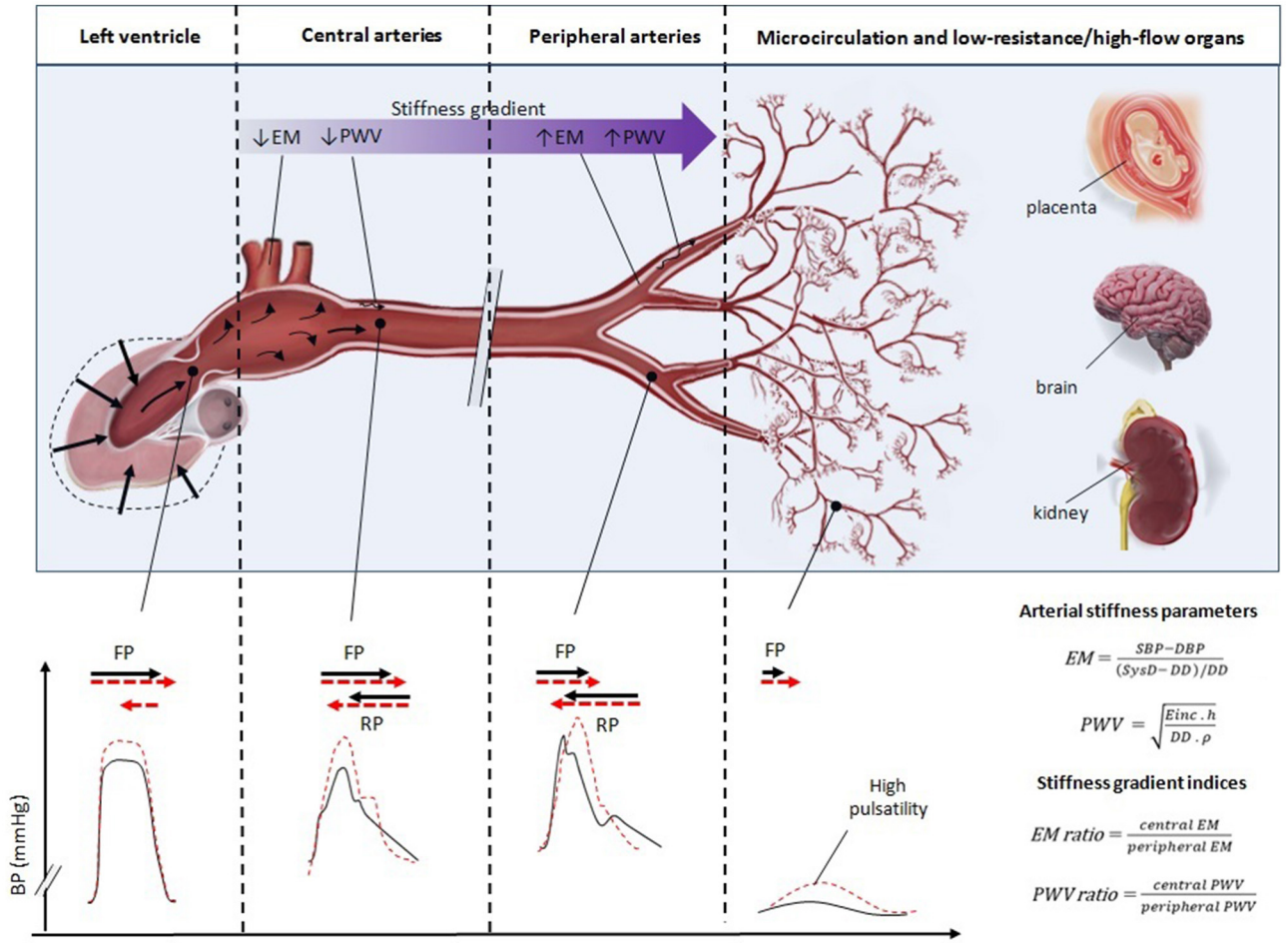

FIGURE 1 | Schematic representation of the interplay between central (e.g., aortic or carotid) and peripheral (e.g., brachial) arterial stiffness in determining the arterial stiffness gradient, partial wave reflection, and distal microcirculatory pressure pulsatility. Normally, the arterial system is characterized by a progressive increase in the arterial stiffness from the aorta to the peripheral arteries ("stiffness gradient"), which can be estimated by PWV (Moens–Korteweg equation), EM and their respective ratios (note that these parameters are inversely determined by the arterial diameter). This gradient creates partial wave reflection [i.e., retrograde pressure waves (RP)] reducing the energy carried peripherally by the forward pressure wave (FP) protecting the microcirculation. With aortic stiffening and/or peripheral maladaptation, the stiffness gradient dissipates (represented by progressive higher levels of PWV and/or EM), the aorta does not optimally distend increasing left ventricle (LV) afterload [represented by increased LV and aortic pressure (dashed red lines)], and increasing the likelihood of high pulsatile energy transmission (dashed red lines) to low-resistance/high-flow vascular beds, such as renal, cerebral, or placental circulation.

local parameters could also offer complementary information in these patients.

This study sought to determine whether HP and PAH are associated with different changes in the physiological center-to-periphery SG assessed by regional (PWV ratio) and local parameters (EM ratio) compared with an NP population. Secondarily, we identified potential differences between the subgroups of PAH (i.e., PE and GH).

MATERIALS AND METHODS

Subjects

This was a cross-sectional study involving non-pregnant and pregnant women from our CUiiDARTE Project database (23–32). The CUiiDARTE Project is a population-based study developed in Uruguay, supported by the National Public Health Ministry and the Agencia Nacional de Investigación e Innovación (ANII). Cardiovascular evaluation in the CUiiDARTE Project involves a stepwise protocol using several equipment and devices that measure central, peripheral, and systemic hemodynamic variables, and structural and functional local, regional, and global properties of elastic, muscular, and transitional arteries (23–32). All procedures and protocols were conducted in agreement with the Declaration of Helsinki, approved by the Institution's Ethics Committee. Written informed consent was obtained prior to the examination.

Healthy NPs ($n = 401$) were selected to be matched for age and global cardiovascular risk factors (CRFs) with the below-mentioned pregnant women. By using propensity score matching methods, efficient matching and balance are created

on the mentioned covariates and their confounding effect can be minimized or entirely removed (13). HP women (n = 10), without known family history of premature cardiovascular disease (CVD), were recruited from the routine antenatal clinic. All women had uncomplicated pregnancies before and during the study. Women with PAH (n = 16) were recruited from the antenatal hospital ward, where they were admitted due to mild hypertension [brachial artery BP (baBP) 140/90–149/109 mmHg].

According to the Bulletin of the American College of Obstetricians and Gynecologists (1), PAH is defined as baBP >140/90 mmHg on two consecutive occasions more than 4 h apart, developing after 20 weeks of gestation in a previously normotensive woman. Depending on whether there was or not significant proteinuria (≥300 mg per 24-h urine collection), patients were further classified as PE or GH, respectively, since all patients included in the study had no evidence of severe features. Laboratory samples were obtained prior to the study enrollment. A clinical interview, together with the anthropometric evaluation [body weight (BW), body height (BH), and body mass index (BMI)] enabled us to assess CRF exposure. A family history of CVD was defined by the presence of first-degree relatives with early CVD (<55 years in men; <65 years in women). Women were categorized as "sedentary" [according to the WHO physical activity (PA) recommendations] if they performed <150 min of moderate-intensity aerobic PA, or <75 min of vigorous-intensity aerobic PA, or an equivalent combination of moderate-intensity and vigorous-intensity PA throughout the week. Dyslipidemia was defined as self-reported or total cholesterol ≥240 mg/dL or HDL cholesterol <46 mg/dL (if available).

Non-Invasive Arterial Evaluation

Subjects were instructed to lie in a left lateral position (to avoid the compression of the inferior vena cava in the case of pregnant women) in a temperature-controlled (21–23°C) room, for at least 10–15 min, to establish a stable hemodynamic condition. Once heart rate (HR) and baBP were stabilized, non-invasive arterial parameters were obtained as described below.

Carotid-to-Femoral PWV, Carotid-to-Radial PWV, and PWV Ratio

Carotid-to-femoral pulse wave velocity and crPWV were non-invasively measured to assess the aortic and upper-limb regional stiffness (SphygmoCor 7.01, AtCor Medical, Sydney, Australia). PWV ratio (regional SG) was calculated as: cfPWV/crPWV (13, 23).

Local Arterial Stiffness and Ratio

Left and right common carotid artery (CCA) and left brachial artery (BA) were analyzed using high-resolution ultrasound (6–13 MHz, MicroMaxx/M-Turbo, Sonosite Inc., WA, USA). CCA and BA blood flow velocity levels and indexes were quantified (26). Sequences of images (30 s, B-Mode, longitudinal views) were processed to obtain peak systolic and end-diastolic diameters (SysD, DD) and CCA intima–media thickness (IMT; far wall, end-diastole) (32). CCA diameters and IMT were measured a centimeter proximal to the bulb, while BA measurements were obtained at the elbow level in a straight segment of at least 1 cm (32). Carotid arteries were also screened for the presence of atheroma plaques (23, 25, 26, 31). Local stiffness was quantified by EM (32):

$$\mathbf{EM} = \frac{(\mathbf{SBP} - \mathbf{DBP})}{(\mathbf{SysD} - \mathbf{DD})/\mathbf{DD}},$$

where SBP and DBP are systolic and diastolic BP. The EM measures the ability of the arteries to change their dimensions in response to the PP caused by the cardiac ejection [pressure change required for (theoretic) 100% increase in diameter]. Oscillometry-derived baSBP and baDBP (HEM-433INT Oscillometric System; Omron-Healthcare Inc., Illinois, USA) were used to quantify BA EM, whereas aortic SBP and DBP (aoSBP, aoDBP) were used to quantify CCA EM. Radial pulse waves were obtained by the applanation tonometry (SphygmoCor 7.01, AtCor-Medical, Sydney, Australia), and calibrated to baDBP and mean BP [MBP = baDBP + (baSBP–baDBP)/3]. The aoSBP and aoDBP were derived from the radial recordings using a general transfer function (30, 32). Finally, local SG was calculated as the quotient between left and right CCA EM (and its average) and BA EM (CCA EM/BA EM).

Data Analysis

Normality of the distribution of the data was examined using the Shapiro–Wilk test and Q–Q plot. The $p < 0.05$ indicates significant statistical differences. One-way analysis of covariance (ANCOVA) with multiple adjusted comparisons was utilized for the evaluation of differences in cardiovascular variables. Demographic characteristics (age), anthropometric (BW, BH, BMI), CRFs exposure, and medication use of the participants were considered as adjustment variables. Considering the relatively small sample sizes of the HP and PAH groups, we performed bootstrapping of the samples, as a strategy to evaluate whether potential statistical differences observed between the study groups maintain even after analyzing different random sampling settings. To this end, bootstrap-derived 95% CIs (1,000 samples) were obtained applying bias-corrected and accelerated methods for computing CI limits (32). In other words, with this mechanism, any initial $p < 0.05$ may no longer be significant after the "fictional random re-sampling" (i.e., bootstrapping). This type of test obligates the investigators to consider only those significant p-values that replicate in both statistical scenarios (i.e., the actual sample and bootstrapping sampling). After performing the comparative analyses between the three primary groups (NP, HP, and PAH), as secondary analysis, we further investigate differences between the four groups (NP, HP, GH, and PE) by discriminating women with PE and GH within the PAH group.

The statistical analyses were performed using the Statistical Package for Social Sciences (version 26.0). All data were presented as mean value (MV) ± standard deviation (SD) or error (SE) of the mean, as well as lower and upper limits (LL and UL, respectively).

TABLE 1 | Demographic, anthropometric, clinical, and cardiovascular characteristics according to the study groups.

	Non-Pregnant women					Healthy pregnant women					Pregnancy-Associated hypertension				
Variables	**MV**	**SD**	**SE**	**Min**	**Max**	**MV**	**SD**	**SE**	**Min**	**Max**	**MV**	**SD**	**SE**	**Min**	**Max**
Age (years)	22.84	5.99	0.30	18	40.7	29.40	6.17	1.95	21.00	40	32.3	6.2	1.6	20.0	40.0
Body weight (kg)	60.75	12.05	0.62	38.10	128.00	67.10	7.32	2.32	56.00	77.00	86.75	15.53	3.88	60.00	113.00
Body height (m)	162.22	6.38	3.25	132.00	183.00	157.60	6.75	2.14	148.00	173.00	159.94	6.93	1.73	149.00	174.00
BMI (kg/m^2)	23.04	4.23	0.22	16.50	48.77	27.13	3.56	1.13	20.72	31.23	34.16	7.12	1.78	21.77	48.27
Hypertension (%)	4.0					0					100				
On BP treatment (%)	1.7					0					12.5				
Dyslipidemia (%)	7.2					20.0					0				
Sedentarism (%)	58.6					100					100				
Peripheral and central hemodynamic parameters															
baSBP (mmHg)	118	11	1	85	177	114	5	2	106	121	127	12	3	98	143
baDBP (mmHg)	69	9	1	49	103	65	10	3	52	85	75	9	2	59	93
Heart rate (bpm)	75	11	1	50	113	81	16	5	52	97	87	13	3	66	110
aoSBP (mmHg)	102	10	1	79	156	100	7	2	90	109	110	11	3	84	126
aoDBP (mmHg)	70	9	1	51	103	67	10	3	55	87	77	9	2	60	94
Carotid and brachial structural and hemodynamic parameters															
Left CCA SysD (mm)	6.61	0.49	0.03	4.84	9.55	7.08	0.39	0.12	6.13	7.49	7.13	0.50	0.12	5.78	7.98
Left CCA DD (mm)	6.04	0.47	0.03	4.39	8.40	6.47	0.42	0.13	5.75	7.19	6.64	0.47	0.12	5.55	7.54
Left CCA IMT (mm)	0.504	0.090	0.005	0.311	1.352	0.527	0.082	0.026	0.422	0.670	0.564	0.095	0.024	0.387	0.774
Left CCA PSV (cm/s)	97.42	19.31	1.09	55.80	191.90	85.15	21.11	10.56	68.50	116.10	93.95	22.88	7.23	59.00	144.60
Left CCA EDV (cm/s)	26.72	5.99	0.34	5.41	49.70	29.35	5.34	2.67	22.20	34.30	25.77	3.65	1.15	20.60	31.70
Left CCA RI	0.72	0.06	0.00	0.55	0.93	0.65	0.09	0.04	0.56	0.72	0.72	0.06	0.02	0.62	0.82
Left CCA SDR	3.78	1.03	0.06	2.20	13.66	2.94	0.70	0.35	2.27	3.58	3.65	0.77	0.24	2.64	5.44
Right CCA SysD (mm)	6.71	0.52	0.03	5.20	9.52	7.10	0.60	0.19	6.07	7.86	7.08	0.57	0.14	5.88	7.90
Right CCA DD (mm)	6.15	0.49	0.03	4.53	8.48	6.49	0.59	0.19	5.58	7.22	6.58	0.52	0.13	5.51	7.49
Right CCA IMT (mm)	0.502	0.084	0.005	0.304	1.218	0.480	0.089	0.028	0.365	0.605	0.597	0.174	0.043	0.335	1.159
Right CCA PSV (cm/s)	93.58	18.91	1.08	50.50	161.60	96.55	38.09	19.05	66.60	152.20	84.86	23.16	6.98	32.70	127.50
Right CCA EDV (cm/s)	25.91	6.47	0.37	9.01	56.60	26.60	2.69	1.34	24.70	30.40	23.45	4.68	1.41	13.70	28.50
Right CCA RI	0.72	0.06	0.00	0.53	0.88	0.70	0.08	0.04	0.60	0.80	0.71	0.07	0.02	0.58	0.79
Right CCA SDR	3.73	0.90	0.05	2.12	8.44	3.57	1.05	0.53	2.50	5.01	3.61	0.73	0.22	2.39	4.79
Left BA SysD (mm)	3.38	0.43	0.06	2.27	4.63	3.80	0.32	0.10	3.11	4.17	4.10	0.47	0.12	3.26	4.72
Left BA DD (mm)	3.21	0.44	0.06	2.02	4.44	3.65	0.34	0.11	2.90	4.05	3.90	0.46	0.11	3.09	4.52
Left BA PSV (cm/s)	75.75	16.89	2.00	37.30	127.10	58.80	16.40	11.60	47.20	70.40	115.99	24.12	9.12	83.70	146.50
Left BA EDV (cm/s)	−2.19	10.97	1.30	−35.30	20.30	15.02	8.32	5.89	9.13	20.90	23.30	6.41	2.42	15.20	34.30
Left BA RI	0.99	0.08	0.01	0.80	1.30	0.76	0.08	0.06	0.70	0.81	0.80	0.04	0.01	0.73	0.84
Arterial stiffness and stiffness gradient parameters															
cfPWV (m/s)	6.48	1.02	0.06	4.10	10.52	5.49	0.69	0.22	4.11	6.58	6.55	0.96	0.24	5.00	8.96
crPWV (m/s)	8.83	1.40	0.12	5.10	12.90	7.18	1.55	0.49	5.24	9.64	6.38	1.07	0.27	4.69	8.21
PWV Ratio	0.71	0.11	0.01	0.49	1.03	0.79	0.17	0.05	0.56	1.05	1.06	0.25	0.06	0.78	1.50
Left BA EM (mmHg)	1,176	729	100	267	3,921	1,445	592	187	591	2,393	1,158	455	114	430	1,978
Left CCA EM (mmHg)	357	116	6	173	831	361	129	43	237	647	502	183	46	246	790
Right CCA EM (mmHg)	364	116	7	173	913	345	69	23	240	438	492	195	49	295	878
Mean CCA EM (mmHg)	360	107	6	188	747	353	93	31	239	529	497	183	46	290	834
Left CCA EM/BA EM	0.43	0.29	0.04	0.06	1.68	0.28	0.17	0.006	0.14	0.63	0.51	0.27	0.07	0.17	1.04
Right CCA EM/BA EM	0.45	0.28	0.04	0.09	1.33	0.26	0.11	0.04	0.14	0.41	0.49	0.26	0.07	0.15	1.07
Mean CCA EM/BA EM	0.44	0.27	0.04	0.09	1.37	0.27	0.14	0.05	0.15	0.51	0.50	0.26	0.07	0.17	1.02

MV, mean value; SD, standard deviation; SE, standard error; Min, minimal value; Max, maximal value; BMI, body mass index; SBP, DBP, systolic and diastolic blood pressure, respectively; ao, aortic; ba, brachial artery; CCA, common carotid artery; BA, brachial artery; SysD, DD, peak systolic and end-diastolic diameter, respectively; IMT, intima-media thickness; PSV, EDV, peak systolic- and end-diastolic velocity, respectively; RI, resistive index; SDR, systo-diastolic ratio; cfPWV, crPWV, carotid-to-femoral and carotid-to-radial pulse wave velocity; PWV, pulse wave velocity; EM, elastic modulus; Sample size, Non-pregnant women (n = 401), Healthy pregnant women (n = 10), Pregnancy-associated hypertension (n = 16).

RESULTS

Regional and Local Arterial Stiffness Gradient of NP, HP, and PAH

Descriptive characteristics and baseline cardiovascular parameters of the study groups are presented in **Table 1** and **Supplementary Table 1**. No women had carotid plaques, diabetes, or family history of premature CVD. Regardless of age and classic CRFs exposure, HP was associated with non-significant changes in PWV ratio compared with NP (assessed by bootstrapping), but with lower levels compared with PAH (**Table 2**). This finding was observed in the presence of significantly lower levels of cfPWV compared with both NP and PAH. HP was also associated with lower levels of crPWV compared with NP, but with only a trend of showing lower crPWV values compared with PAH (*p*: 0.06–0.08; **Table 2**).

When considering EM ratio, a general trend of lower values was observed in HP when compared with NP women, although no clear differences were observed when comparing with PAH (**Table 2**). HP showed significantly lower levels of CCA EM compared with PAH, without clear differences when compared with NP. No differences were observed in the BA EM compared with NP or PAH. Finally, HP showed higher levels of BA and CCA diameters than NP and was similar to PAH (**Table 2**). In summary, when comparing with NP status, HP was associated with a drop in the AS in both territories, evidenced by both regional (cfPWV and crPWV) and local (except for BA EM) stiffness-related parameters, without significant changes in PWV ratio (i.e., bootstrapping) but a reduction in CCA EM/BA EM.

PAH was associated with an increased in the PWV ratio that exceeded the levels of both NP and HP (**Table 2**). The rise in PWV ratio was explained by a lower (although significant) reduction of cfPWV levels with respect to that observed in HP with respect to NP, and a higher reduction in the levels of crPWV with respect to those observed between HP and NP. The greater drop in crPWV levels was followed by a trend toward higher levels in BA diameters (although not significant with respect to HP). The observed blunted reduction in cfPWV values in women with PAH coincided with an increase in the CCA EM compared with NP and HP (**Table 2**).

Subgroup Analysis of PAH (Gestational Hypertension and Pre-Eclampsia)

When performing a subgroup analysis of women with PAH (**Supplementary Table 1**), the elevated stiffness ratio in PAH was mainly driven by the changes in arterial stiffness observed in those women with PE (**Table 3**). Indeed, although higher PWV ratio values were observed in GH compared to HP, these findings did not show statistical significance ($p = 0.069$ and $p = 0.064$; **Table 3**). However, women with PE were associated with exaggerated increase in PWV ratio compared with all other groups. PE showed higher and lower levels of cfPWV and crPWV, respectively, compared to GH ($p < 0.05$). Moreover, crPWV was found significantly reduced in women with PE compared with the other groups, where NP, HP, GH, and PE showed a descending order of crPWV values (**Table 3**). Women complicated with PE demonstrated higher levels of cfPWV compared with HP and GH, but similar to NP. Of note, the GH group showed a trend toward higher levels of PWV ratio and cfPWV compared with HP (*p*-values: 0.05–0.07; **Table 3**). Otherwise, GH presented similar values in almost all other analyzed parameters when compared to HP, while having similar differences with respect to NP.

While PE showed elevated CCA EM *vs*. other groups (even comparing with GH), GH did not show significant differences in this parameter when compared to NP or HP (**Table 3**). In other words, this pregnancy status did not show the characteristic PE-associated increase in CCA stiffness or the HP-associated reduction in CCA stiffness. At the level of the BA, even though PE showed a trend toward higher BA stiffness, this finding did not reach statistical significance when compared with the other study groups (**Table 3**). Finally, CCA EM/BA EM, which was reduced in HP compared with NP, was similar between GH and PE vs. NP, although PE presented higher numerical values.

DISCUSSION

The present study is, to our knowledge, the first one to determine and compare, in a group of healthy non-pregnant and pregnant women with and without hypertensive disorders of pregnancy, the arterial SG by using different but complementary approaches considering central, peripheral, regional, and local arterial parameters. The main contributions of this study are:

First, when compared with NP status, HP was associated with unchanged PWV ratio but with a reduction in CCA EM/BA EM, in the setting of a generalized decrease in AS.

Second, when compared with NP and HP, PAH was associated with an "exaggerated rise" in the PWV ratio without any change in CCA EM/BA EM, in the setting of a blunt reduction in cfPWV and exaggerated crPWV reduction.

Third, the attenuation or even reversal of the central-to-peripheral SG observed in PAH was mainly driven by the changes in arterial stiffness observed in those women with PE.

Healthy Pregnancy

While changes in central arteries have been largely described in different studies, changes in the peripheral AS have been inconclusive. Resting crPWV, which assesses mainly the upper limb AS (i.e., mostly muscular arteries), was found to be reduced in uncomplicated pregnant women in some (19, 33, 34) but not in all studies (20, 35, 36). Pregnancy-related changes in peripheral AS may also change over the course of the pregnancy (34).

In the present cross-sectional study, we found that both cfPWV and crPWV in HP were lower than those of NP in the third trimester. In addition, HP was also characterized by an increase in arterial diameters and a trend of showing lower local stiffness values (mainly CCA EM), all of which can explain the reduced regional AS. Despite these observations, the PWV ratio remained largely unchanged compared to NP (assessed by bootstrapping) because the relative reduction in both parameters seems to be counterbalanced. However, CCA EM/BA EM did show a significant reduction compared to NP. As previously mentioned, it has been demonstrated that the SG in normal non-pregnant populations works as

TABLE 2 | Regional and local arterial stiffness and gradient: comparison after adjustments (ANCOVA).

		After Adjustment				Pair wise Comparisons			
Variable	**Group**	**MV**	**SE**	**LL**	**UL**		**NP vs. HP**	**NP vs. PAH**	**HP vs. PAH**
Regional arterial stiffness and gradient									
PWV ratio	NP	0.71	0.01	0.69	0.74	*p*	0.046	<0.001	<0.001
	HP	0.80	0.05	0.71	0.89	Boot. *P*	0.060	<0.001	0.003
	PAH	1.05	0.04	0.97	1.13		–	–	–
cfPWV (m/s)	NP	6.51	0.05	6.41	6.61	*p*	<0.001	0.017	0.014
	HP	5.16	0.29	4.59	5.74	Boot. *P*	<0.001	0.025	0.004
	PAH	5.99	0.24	5.52	6.46		–	–	–
crPWV (m/s)	NP	8.95	0.12	8.72	9.18	*P*	<0.001	<0.001	0.077
	HP	6.59	0.45	5.69	7.48	Boot. *P*	<0.001	<0.001	0.066
	PAH	5.77	0.39	5.00	6.53		–	–	–
Local arterial stiffness and gradient									
Left BA DD (mm)	NP	3.20	0.06	3.08	3.33	*P*	0.003	<0.001	0.178
	HP	3.68	0.16	3.37	3.99	Boot. *P*	0.002	<0.001	0.165
	PAH	3.87	0.12	3.63	4.11		–	–	–
Right CCA DD (mm)	NP	6.14	0.03	6.09	6.20	*P*	0.051	0.003	0.308
	HP	6.40	0.16	6.10	6.71	Boot. *P*	0.099	0.005	0.344
	PAH	6.50	0.13	6.25	6.75		–	–	–
Left CCA DD (mm)	NP	6.04	0.03	5.99	6.09	*p*	0.015	<0.001	0.218
	HP	6.37	0.15	6.08	6.67	Boot. *P*	0.009	<0.001	0.211
	PAH	6.52	0.12	6.28	6.76		–	–	–
Mean CCA EM/BA EM	NP	0.46	0.04	0.39	0.53	*p*	0.071	0.415	0.147
	HP	0.31	0.09	0.13	0.49	Boot. *P*	0.046	0.400	0.092
	PAH	0.44	0.07	0.30	0.57		–	–	–
Left CCA EM/BA EM	NP	0.45	0.04	0.38	0.53	*P*	0.123	0.460	0.192
	HP	0.33	0.10	0.14	0.52	Boot. *P*	0.097	0.459	0.144
	PAH	0.44	0.07	0.30	0.59		–	–	–
Right CCA EM/BA EM	NP	0.46	0.04	0.39	0.53	*p*	0.050	0.379	0.129
	HP	0.29	0.09	0.11	0.48	Boot. *P*	0.041	0.372	0.106
	PAH	0.44	0.07	0.30	0.57		–	–	–
Left CCA EM (mmHg)	NP	360.51	5.95	348.80	372.23	*p*	0.156	0.023	0.010
	HP	308.81	35.83	238.32	379.30	Boot. *P*	0.117	0.122	0.033
	PAH	425.71	27.74	371.15	480.28		–	–	–
Right CCA EM (mmHg)	NP	368.18	5.91	356.54	379.81	*p*	0.078	0.011	0.005
	HP	282.65	35.36	213.09	352.20	Boot. *P*	0.058	0.061	0.016
	PAH	416.39	27.33	362.63	470.15		–	–	–
Left BA EM (mmHg)	NP	1,158.85	92.37	974.67	1,343.03	*P*	0.374	0.218	0.400
	HP	1,239.06	230.37	779.71	1,698.40	Boot. *P*	0.366	0.133	0.381
	PAH	1,318.20	178.89	961.50	1,674.90		–	–	–

MV, mean value; SE, standard error; 95% CI, 95% confidence interval; LL, lower limit; UL, upper limit; Boot, bootstrapping; NP, non-pregnant women (n = 401); HP, healthy pregnant women (n = 10); PAH, pregnancy-associated hypertension (n = 16); CCA, common carotid artery; BA, brachial artery; DD, end-diastolic diameter; cfPWV, crPWV, carotid-to-femoral and carotid-to-radial pulse wave velocity; PWV, Pulse wave velocity; EM, elastic modulus.

a filter of excessive pressure energy transmission to certain microcirculatory beds (22). Thus, from a physiologic standpoint, the increased dampening function of the maternal aorta and the preservation of the SG would both have enhanced protective effects on the distal microcirculation limiting barotrauma and excessive shear forces, which would occur in an otherwise not adapted cardiovascular system to increase blood flow regimen (5, 33).

Pregnancy-Associated Hypertension

On the other hand, in comparison with HP, both subgroups of PAH showed, although with different magnitudes, greater increments in both arterial diameters and CCA EM (BA EM was unchanged), along with a lower/blunted reduction in cfPWV and a higher elevation in PWV ratio. The higher cfPWV of PAH compared to HP suggests that the pregnancy-induced healthy decrease in the aortic stiffness did not occur in this group of

TABLE 3 | Regional and local arterial stiffness and gradient: comparison after adjustments (ANCOVA: 4 groups).

Variable	Group	MV	SE	LL	UL		NP vs. HP	NP vs. GH	NP vs. PE	HP vs. GH	HP vs. PE	GH vs. PE
Regional arterial stiffness and gradient												
PWV ratio	NP	0.71	0.01	0.69	0.74	*P*	0.027	<0.001	<0.001	0.069	<0.001	<0.001
	HP	0.80	0.04	0.72	0.89	Boot. *P*	0.044	<0.001	0.001	0.064	0.001	0.002
	GH	0.90	0.05	0.80	0.99		–	–	–	–	–	–
	PE	1.22	0.05	1.12	1.32		–	–	–	–	–	–
cfPWV (m/s)	NP	6.51	0.05	6.41	6.61	*P*	<0.001	0.002	0.402	0.177	0.002	0.028
	HP	5.17	0.29	4.59	5.74	Boot. *P*	<0.001	<0.001	0.418	0.059	0.001	0.019
	GH	5.57	0.32	4.93	6.21		–	–	–	–	–	–
	PE	6.42	0.33	5.78	7.07		–	–	–	–	–	–
crPWV (m/s)	NP	8.95	0.12	8.72	9.18	*P*	<0.001	<0.001	<0.001	0.321	0.022	0.059
	HP	6.57	0.45	5.68	7.46	Boot. *P*	<0.001	<0.001	<0.001	0.301	0.018	0.010
	GH	6.27	0.50	5.28	7.25		–	–	–	–	–	–
	PE	5.22	0.52	4.20	6.25		–	–	–	–	–	–
Local arterial stiffness and gradient												
Left BA DD (mm)	NP	3.20	0.06	3.08	3.33	*P*	0.003	0.002	<0.001	0.415	0.072	0.087
	HP	3.68	0.15	3.37	3.98	Boot. *P*	0.001	0.003	0.001	0.417	0.061	0.093
	GH	3.73	0.16	3.41	4.05		–	–	–	–	–	–
	PE	4.03	0.17	3.70	4.36		–	–	–	–	–	–
Right CCA DD (mm)	NP	6.14	0.03	6.09	6.20	*P*	0.051	0.054	0.007	0.461	0.223	0.259
	HP	6.40	0.16	6.10	6.71	Boot. *P*	0.087	0.076	0.009	0.468	0.247	0.258
	GH	6.43	0.17	6.09	6.77		–	–	–	–	–	–
	PE	6.58	0.18	6.24	6.93		–	–	–	–	–	–
Left CCA DD (mm)	NP	6.04	0.03	5.99	6.09	*P*	0.015	0.003	0.002	0.271	0.234	0.454
	HP	6.37	0.15	6.08	6.67	Boot. *P*	0.015	<0.001	0.013	0.204	0.258	0.454
	GH	6.51	0.17	6.18	6.84		–	–	–	–	–	–
	PE	6.54	0.17	6.20	6.87		–	–	–	–	–	–
Mean CCA EM/BA EM	NP	0.46	0.04	0.39	0.53	*P*	0.070	0.214	0.313	0.309	0.080	0.155
	HP	0.31	0.09	0.13	0.49	Boot. *P*	0.045	0.119	0.312	0.251	0.066	0.129
	GH	0.38	0.09	0.20	0.56		–	–	–	–	–	–
	PE	0.50	0.09	0.32	0.69		–	–	–	–	–	–
Left CCA EM/BA EM	NP	0.45	0.04	0.38	0.53	*P*	0.123	0.281	0.329	0.337	0.126	0.208
	HP	0.33	0.10	0.13	0.52	Boot. *P*	0.100	0.208	0.346	0.294	0.113	0.185
	GH	0.39	0.10	0.20	0.58		–	–	–	–	–	–
	PE	0.50	0.10	0.30	0.70		–	–	–	–	–	–
Right CCA EM/BA EM	NP	0.46	0.04	0.39	0.53	*P*	0.049	0.176	0.314	0.300	0.064	0.131
	HP	0.29	0.09	0.10	0.48	Boot. *P*	0.039	0.081	0.311	0.237	0.059	0.097
	GH	0.37	0.09	0.18	0.55		–	–	–	–	–	–
	PE	0.51	0.10	0.32	0.70		–	–	–	–	–	–
Left CCA EM (mmHg)	NP	360.43	5.88	348.86	372.01	*P*	0.079	0.382	<0.001	0.220	<0.001	0.001
	HP	309.43	35.41	239.77	379.09	Boot. *P*	0.055	0.399	0.005	0.222	0.002	0.017
	GH	349.04	37.46	275.36	422.72		–	–	–	–	–	–
	PE	504.85	38.02	430.06	579.64		–	–	–	–	–	–
Right CCA EM (mmHg)	NP	368.08	5.79	356.68	379.47	*P*	0.008	0.101	<0.001	0.231	<0.001	<0.001
	HP	283.40	34.64	215.25	351.54	Boot. *P*	<0.001	0.100	0.015	0.193	0.001	0.006
	GH	320.46	36.62	248.42	392.50		–	–	–	–	–	–
	PE	515.32	37.16	442.22	588.42		–	–	–	–	–	–
Left BA EM (mmHg)	NP	1,158.63	93.00	973.14	1,344.11	*P*	0.375	0.317	0.232	0.450	0.373	0.414
	HP	1,238.58	231.94	775.98	1,701.17	Boot. *P*	0.360	0.269	0.122	0.439	0.332	0.347
	GH	1,282.95	241.44	801.42	1,764.48		–	–	–	–	–	–
	PE	1,355.46	247.64	861.55	1,849.36		–	–	–	–	–	–

MV, mean value; SE, standard error; 95% CI, 95% confidence interval; LL, Lower limit; UL, upper limit; Boot, bootstrapping; NP, non-pregnant women (n = 401); HP, healthy pregnant women (n = 10); GH, gestational hypertension (n = 8); PE, pre-eclampsia (n = 8); CCA, common carotid artery; Brachial artery. DD, end-diastolic diameter; cfPWV, crPWV, carotid-to-femoral and carotid-to-radial pulse wave velocity; PWV, pulse wave velocity; EM, elastic modulus.

patients ("impaired de-stiffening effect"). Of note, cfPWV in PAH was still significantly reduced compared to NP, a finding that was likely determined by an equilibrium between (i) larger diameters of central arteries (e.g., CCA) mainly present in women with PE (i.e., the larger arterial dimensions, the lower PWV; explained by Moens–Korteweg equation) and (ii) higher local AS found in both CCA [the higher EM, the higher PWV (Moens–Korteweg equation)] (**Figure 1**). The overall augmentation trend of arterial diameters in PAH could be an arterial compensatory response and/or BP dependent, and possibly, could be the reason behind the significant drop in crPWV levels when comparing PAH and NP. All these findings together determine that in PAH (but mostly in PE women) PWV and EM ratios become elevated (being in the latter case in the limit of significance). Regardless, the observed reduction in CCA EM/BA EM in HP compared to NP was not found in women with PAH compared to HP. Of note, when performing subgroup analysis in the group of women with PAH (**Table 3**), the blunt reduction in cfPWV values, the reduction in crPWV and the center-to-periphery arterial SG attenuation and/or reversal observed in the PAH group were mainly determined by women with PE. Strikingly, PE showed similar cfPWV values compared to NP, a detrimental finding in the setting of pregnancy, in where there is an expected 30 and 50% physiologic increase in SV and CO, respectively, to meet the increased metabolic needs of the developing fetus (37). This suggests that the aorta would not distend properly in the setting of the increase in effective circulating volume, or it would do it but at the expense of elevated aoBP. Moreover, a relative stiff aorta would provoke reflected pressure waves to travel faster from the periphery to the ascending aorta during the late systolic phase imposing inappropriate loads to LV. In non-pregnant populations, the increased aoBP, aortic stiffness, and pulsatile forward pressure wave in hypertensive patients have been shown to be associated with increased renal blood flow pulsatility, thereby explaining the association between PP, microalbuminuria, and renal microvascular damage (37). Similarly, Mitchell et al. reported that increased aortic stiffness and reduced wave reflection at the carotid-aorta interface were associated with excessive flow pulsatility, microvascular structural brain damage, and lower scores in various cognitive domains (14). Furthermore, the PWV ratio has shown independent clinical predictive value in different pathophysiologic circumstances, having this parameter higher prognostic value than cfPWV itself (11–13, 22).

The arteriolar network is a major site of resistance and reflections and the ultimate microcirculation protection against barotrauma and excessive shear forces. The loss of the SG has been associated with endothelial dysfunction, vascular myogenic response, and impaired organ perfusion (12). Thus, if the maternal arterial system suffers a loss or reversal of arterial SG (aortic PWV > peripheral PWV), pulsatile pressure could be either filtered by an increased arteriolar myogenic response but at the expense of reducing the blood flow or would not be sufficiently dampened and filtered damaging the distal microcirculation. Given the fetal metabolic needs, the placenta must operate at very high flow/low vascular resistance being second only to the kidney regarding blood flow rates per unit of tissue mass (8). Other low-resistance vascular beds, such as renal, hepatic, and cerebral circulation are also at risk of excessive pulsatility since microvascular pressure is also directly coupled with aoBP fluctuations (8) (**Figure 1**). Hence, the transmission of a higher pulsatile pressure into the placental and other low-resistance microcirculations might be highly likely in the setting of attenuation or reversal of SG. Taken together, the loss and/or reversal of arterial SG throughout the arterial tree could have a major role in the pathophysiology and clinical manifestations of PE, leading to secondary placental dysfunction (e.g., intrauterine growth restriction), renal (e.g., proteinuria) and hepatic damage (e.g., elevated liver enzymes, hematoma), and in other severe cases, cerebral dysfunction (5).

Clinical and Physiological Relevance

The maternal arterial system during normal pregnancy, characterized by high metabolic needs and a high-flow state, requires not only a low peripheral vascular resistance but also an overall reduction in AS (central and peripheral) with preservation of the SG. This arterial adaptation would likely play a major role in facilitating adequate damping and filtering of excessive forward and reflected waves, optimization of BP, LV static and dynamic afterload, and microvascular network perfusion. Conversely, in PAH, and particularly PE, aortic stiffness does not decrease as physiologically required, and along with possible detrimental maladaptation of the peripheral arteries, dissipating the normal expected SG.

The loss or reversal of the SG, demonstrated to be deleterious in non-pregnant populations, would likely jeopardize the microcirculation in women with PAH, potentially leading to increased vascular myogenic response, endothelial dysfunction, and impaired organ perfusion. This arterial maladaptation syndrome observed in women with PAH could ultimately explain that obligate high-flow organs in the maternal circulation such as the kidneys, brain, and placenta are more susceptible to the adverse effects of the loss of SG having a potential role in the pathophysiology and clinical manifestations of PE.

Strengths and Limitations

Our results should be analyzed in the context of strengths and limitations. To the best of our knowledge, there are no studies in the literature that have evaluated the SG in pregnant women complicated with PAH. Another important strength of this study is the robustness of the methodology employed to assess AS and its SG. We perform a comprehensive evaluation of AS (such as analysis of regional and local parameters) by using simple, non-invasive, robust, and reproducible methods. The use of applanation tonometry has been largely validated and PWV is regarded as the gold standard method for measuring regional AS. Regarding local stiffness and its gradient, we used a combination of high-resolution ultrasound and BP. In the latter case, in this study, aortic, and brachial BP was used to quantify central and peripheral AS levels, respectively. This should be considered as a strength since previous studies have quantified CCA stiffness by using brachial PP, which could lead to inaccuracies of the parameters.

This study has certain limitations. First, the sample size of our group of pregnant women is relatively small. To overcome this limitation, we used bootstrapping, a statistical method that creates a new sample of observations of the variables by randomized re-sampling with replacement based on the original observations. Although this method has its own advantages and disadvantages, even in this context, the biggest mistake we can make is not to generate a type I error (finding differences when in fact there are no differences), but to generate a type 2 error (not finding differences when in fact there are differences). Consequently, we have been "conservative," in the fact that we may miss significant differences in cases where potentially there are. Second, since this is a cross-sectional study, it provides no data on longitudinal pregnancy-related temporal variations in variables of interest. Prospective studies are clinically needed to assess whether women showing a reversal of PWV ratio or absence of CCA EM/BA EM reduction are at risk of developing obstetric complications. Third, in this work, the concept of SG was presented as "static or unchanged," rather than the composite of (i) "fixed or stable" [e.g., age-dependent vascular (intrinsic) stiffness level] and (ii) "variable or adjustable" (e.g., endothelial and vascular smooth muscle ability to temporally adjust the AS levels) (38). The systematization of recording conditions is necessary to evaluate AS-related parameters considering the existence of modulating factors. In this work, to systematize the measurement and to minimize the impact of sources of variability, AS levels were determined at rest, under stable hemodynamic conditions.

CONCLUSIONS

Compared with NP status, HP was associated with unchanged PWV ratio but with a reduction in CCA EM/BA EM, in the setting of a generalized decrease in AS.

Compared with NP and HP, PAH was associated with an "exaggerated rise" in the PWV ratio without any change in CCA EM/BA EM, in the setting of a blunt reduction in cfPWV and exaggerated crPWV reduction.

The attenuation or even reversal of the SG observed in PAH was mainly driven by the changes in arterial stiffness observed in those women with PE.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Centro Hospitalario Pereira-Rossell Ethic Committee and Hospital de Clínicas. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MP, JT, DB, and YZ contributed to the conception and design of the study. JT, YZ, and DB performed the cardiovascular non-invasive recordings and constructed and organized the database. YZ and DB performed the statistical analysis. MP, JT, DB, and YZ wrote the first draft of the manuscript. CS and AD performed revisions and critically discussed the complete manuscript. All authors, read, and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2021.766723/full#supplementary-material

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Pregnancy Complications and Outcomes Among Women With Congenital Heart Disease in Beijing, China

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Objective: To conduct a comparative analysis of the complications and outcomes in pregnant women with and without congenital heart disease (CHD) in Beijing, China.

Methods: We compared pregnancy-related complications and outcomes experienced by women with and without CHD throughout 19,424 deliveries in Beijing Anzhen Hospital between 2010 and 2019, including cardiovascular and obstetric factors, fetal events, delivery methods, and other complications over a mean 5-years post-delivery follow-up period.

Results: There were 1,040 women with CHD (5.35% of all deliveries). Compared to women without CHD, these women had longer hospital stays (7.83 ± 4.65 vs. 4.93 ± 3.26 days) and a higher death rate (1.92 vs. 0.02%). They also had a greater risk of comorbidities, including pre-term delivery (odds ratio: 13.65 vs. 6.71), heart failure (odds ratio: 4.90 vs. 0.40), and arrhythmia (odds ratio 12.69 vs. 4.69). Pulmonary hypertension, New York Heart Association functional class III∼IV, and no congenital heart disease surgery prior to pregnancy were associated with adverse events such as cesarean section, pre-term delivery, and heart failure. The fetuses of mothers with CHD were more likely to be born pre-term (odds ratio: 13.65 vs. 6.71) and have low birth weight (odds ratio: 8.56 vs. 4.36). Eleven infants (1.82%) born to mothers with CHD and four infants (0.64%) born to mothers without CHD were diagnosed with CHD.

Conclusions: Women with CHD generally increase maternal and infant risk during pregnancy and the perinatal period. Pulmonary hypertension, decrease in cardiac function, and no previous CHD surgery increase the risk in women with CHD. Greater attention should be paid to pregnant women with CHD and their fetuses, newborns.

Keywords: congenital heart disease, pulmonary hypertension, heart failure, pregnancy, woman

INTRODUCTION

Due to improvements in surgical techniques and the effectiveness of intensive care, more and more individuals with CHD reach adulthood (1). The number of adults with CHD is increasing every year, resulting in a significant increase in the number of pregnant women with CHD, thereby increasing the burden on the medical system (2). At the same time, the incidence of complications in fetuses and newborns of pregnant women with CHD may also be higher (3). Therefore, pregnancies in women with heart disease are considered high-risk, and more attention is being paid to pregnant women with CHD.

In 2007, Beijing Anzhen Hospital was designated as the Referral and Consultation Center of Pregnancy with Heart Diseases in Beijing. Many pregnant women with heart disease went to Beijing Anzhen Hospital for consultations and treatment. Some were also referred to this hospital because of heart complications during pregnancy, where CHD was the most common culprit. What needs illustration is that the vast majority of mothers were healthy.

There are few large sample studies on complications in pregnant women with CHD (4), and the effect of pregnancy on long-term health and the mechanisms that contribute to poor fetal and neonatal outcomes are poorly understood (5). Meanwhile, the influence of the following factors that may influence pregnant women or their babies are worthy of exploration: (1) the degree of pulmonary hypertension (PH); (2) New York Heart Association (NYHA) functional class; (3) whether or not an individual previously underwent CHD surgery; and (4) the severity of CHD. It is of significant importance to study the maternal complications associated with CHD to determine whether these women and their fetuses require additional medical care.

The aim of the current study was to compare the complications and outcomes in pregnant women with and without CHD. A comparative analysis of pregnant women with CHD was also conducted based on the following factors: (1) presence or absence of PH; (2) NYHA functional class III∼IV versus I∼II; (3) history of CHD surgery or not; and 4) the severity of CHD. Adverse events were also analyzed in women with CHD and their offspring.

MATERIALS AND METHODS

Study Design

Data of pregnant women with and without CHD were collected between January 1, 2010 and December 31, 2019. Study data on cardiovascular and obstetric characteristics, fetal events, delivery method, and other events during hospitalization were collected from the statistical office and information center of Beijing Anzhen Hospital. In order to avoid detection bias, we only analyzed complications that occurred from the last admission if the pregnant woman had several admissions. Hospital cost was calculated from the day of admission to the day of discharge, and this information was taken directly from the Inpatient Case Register. Some of the observational data were extracted from physical records or obtained by telephone interviews. Women who did not give birth (interruptions for medical reasons or abortions) were not included, as we could not obtain a full complement of data. A few pregnant women who visited our obstetrics department for early treatment but finally went to other hospitals for delivery were also excluded. Data of pregnant women who underwent surgery for other non-congenital heart diseases, such as rheumatic mitral valve disease requiring mitral valve replacement, were also excluded. The data collection flowchart is shown in **Figure 1**.

Pregnant women with CHD and their offspring were followed up for more than 1 year after hospital discharge. Given that the workload would have been enormous if we followed up all women without CHD, we selected a random sample. The ratio between the two groups was about 1:1. Follow-up was conducted via telephone and outpatient visits. Information obtained on mothers included maternal death, PH, heart failure (HF), arrhythmias, activity limitations, and medical treatment. Information obtained on offspring included death, growth restriction, CHD, and mental developmental delay. We used the same methods during the follow-up after delivery as were used during pregnancy and delivery.

Definitions

A major adverse cardiac event was defined as a pregnancy-related complication in women with and without CHD. Cardiovascular complications included arrhythmias, HF, and thromboembolic events such as stroke and pulmonary embolism. Examined obstetric complications were hypertension during pregnancy, gestational diabetes, preeclampsia, pre-term delivery, hemorrhage, placental abruption, placenta previa, and prolonged pregnancy. Fetal complications of interest included fetal malformation, fetal distress, fetal death or stillbirth, and fetal growth restriction. Delivery events examined included cesarean section, induction, and artificial rupture of the membranes. Other comorbidities were respiratory/pulmonary diseases, systemic hypertension, hyperlipidemia, mental health, and neurologic/central nervous system diseases. We considered events such as HF, PH, pre-term delivery, and low birth weight to be of primary importance.

In order to avoid prevalence-incidence bias in our study, we considered PH as a concomitant disease rather than as a complication, given that many patients had pre-existing PH before pregnancy due to heart disease. PH was defined by an increase in invasively measured mean pulmonary arterial pressure $\geq$25 mmHg at rest. The diagnosis of PH was mostly made by echocardiography, and we also defined PH as an estimated pulmonary systolic pressure of more than 40 mmHg. The degree of PH was determined according to tricuspid regurgitation velocity and tricuspid cross valve pressure difference, and some of the patients underwent right cardiac catheterization. Most of the events, such as PH and Eisenmenger syndrome, were defined according to the european society of cardiology guidelines on CHD. HF was defined according to the european society of cardiology guidelines on acute and chronic heart failure. Obstetric/gynecological and pediatric events were also defined according to the guidelines. The cardiac functional class was graded according to NYHA. In addition, the severity

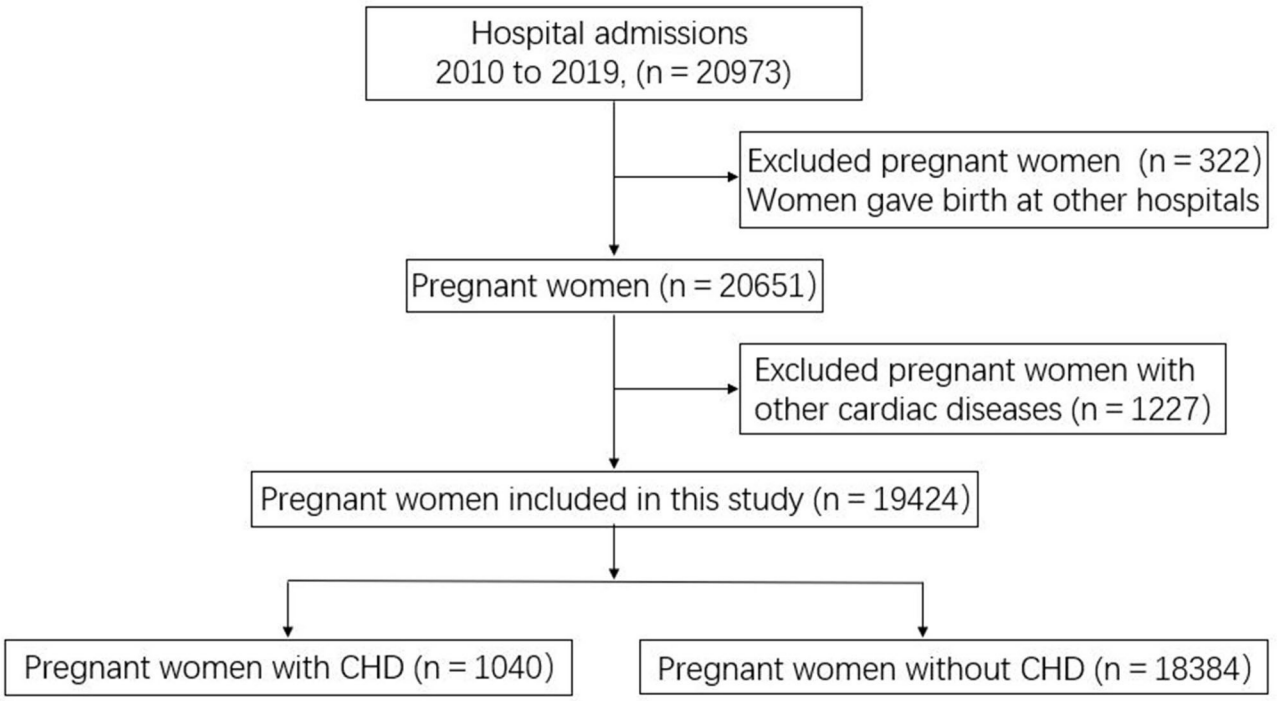

FIGURE 1 | Flowchart of data collection for pregnant women with and without CHD.

of CHD was determined according to the description by Osteen et al. (5) (**Supplementary Table 1**).

Ethical Approval

All procedures performed in this study were in accordance with the ethical standards of the research committee of Beijing Anzhen Hospital affiliated with Capital Medical University and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This study was approved by the research committee of Beijing Anzhen Hospital affiliated with Capital Medical University, who permitted the collection of data for audit and research purposes.

Statistical Analysis

Bivariable analyses were used to examine demographic differences between women with and without CHD. Standard deviations were reported for continuous variables, and the mean values were calculated. The chi squared test was used for categorical variables. The normality of the variables was analyzed using the Kolmogorov-Smirnov test and Shapiro-Wilk test. Logistic regression was used to calculate crude odds ratios and adjusted odds ratios (aORs) and the 95% confidence intervals for each comorbidity, as well as cardiovascular, obstetric, fetal, and delivery-related factors, and other events. Initially, we performed univariable analysis, and a multivariable logistic regression analysis was performed for variables with $P < 0.1$. For pregnant women with and without CHD, analyses of complications and outcomes were conducted. At the same time, analyses were conducted among pregnant women with CHD with or without PH, according to NYHA functional class, history of previous surgery, and severity of CHD. The subgroup analysis was adjusted for multiple comparisons using the Bonferroni correction method. For all analyses, statistical significance was assigned based on a p-value of < 0.05. Model fit was evaluated using deviance and Pearson's statistical tests. All statistical analyses were conducted using SPSS v. 22.0 (IBM-SPSS Statistics Inc., Chicago, IL) and R version 4.0.4 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

A total of 19,424 deliveries occurring at Beijing Anzhen Hospital between January 1, 2010 and December 31, 2019 were included in this study. Among women admitted for delivery, 1,040 (5.35%) had a diagnosis of CHD. The most common type of CHD was atrial septal defect (32.88% of CHD deliveries) (**Figure 2** and **Supplemental Table 2**). Patients came to the hospital from both urban and rural areas (**Supplemental Table 3**).

The most common complications and outcomes in pregnant women with CHD were PH (26.06%), pre-term delivery (13.65%), gestational diabetes (13.37%), hemorrhage (13.17%), arrhythmia (12.69%), and infants with low birth weight (8.56%). There were statistically significant differences between the two groups for most events, such as length of hospital stay (days) and death (**Table 1**).

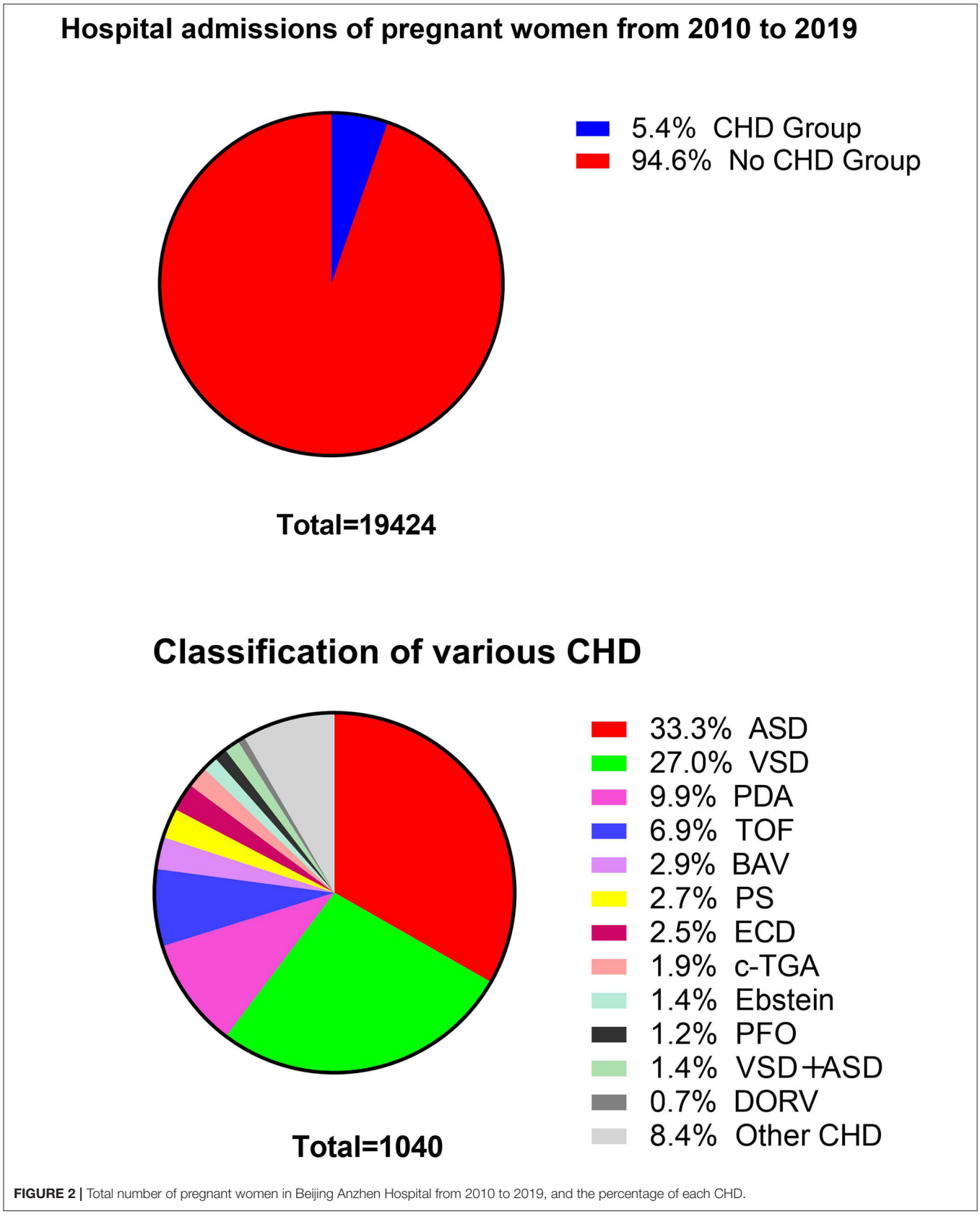

FIGURE 2 | Total number of pregnant women in Beijing Anzhen Hospital from 2010 to 2019, and the percentage of each CHD.

TABLE 1 | Demographic characteristics of women with and without CHD admitted for delivery, 2010 to 2019.

	CHD (*n* = 1,040)	No CHD (*n* = 18,384)	*p* Value
Age, yrs	28.77 ± 4.34	30.42 ± 3.82	<0.001
15–19	4(0.38)	15 (0.08)	
20–24	153 (14.71)	726 (3.95)	
25–29	462 (44.42)	7,357 (40.02)	
30–34	291 (27.98)	7,694 (41.85)	
35–39	90 (8.65)	2,233 (12.15)	
≥40	40 (3.85)	359 (1.95)	
Hospital stay (days)	7.83 ± 4.65	4.93 ± 3.26	<0.001
Hospitalized times ≥2	393 (37.79)	4,613 (25.09)	<0.001
Death	20 (1.92)	4 (0.02)	<0.001
Total charges, $	1,536.78 ± 1,075.39	960.08 ± 789.98	<0.001

CHD, congenital heart disease; yrs, years; Values are mean ± SD, n (%), or median (interquartile range). The symbol $ means U.S. dollar.

Adverse Events in Pregnant Women With and Without CHD

The aORs for most obstetric events, cardiovascular events, delivery method, and fetal events such as placental abruption, pre-term delivery, HF, arrhythmia, cesarean section, growth restriction, and low birth weight, were significantly greater in pregnant women with CHD than in pregnant women without CHD. However, the aORs for some events, including fetal distress, gestational diabetes, and hemorrhage were significantly lower among pregnant women with CHD than among pregnant women without CHD. There was no difference in the risk of placenta previa, preeclampsia, or prolonged pregnancy between the two groups (**Table 2**).

The probability of HF occurring in pregnant women with CHD was12.25times than HF in pregnant women without CHD (4.9 vs. 0.4%; $P < 0.001$). The probability of PH was 48.26 times higher in women with CHD (26.06 vs. 0.54%; $P < 0.001$). The probability of cardiac arrhythmia, pre-term delivery, low birth weight, and cesarean section was alsomuch higher in CHD group (all $P < 0.001$) (**Figure 3**).

Adverse Events in Pregnant Women With CHD by Subgroup (PH, NYHA, Surgery, Severity)

In women with CHD and PH, the aORs for pre-term delivery, HF, cesarean section, infant of low birth weight, and respiratory/pulmonary diseases were significantly greater than in pregnant women with CHD but without PH (all $P < 0.05$). Pregnant women with CHD and PH had significantly lower risk of artificial rupture of the membranes than women with CHD without PH ($P < 0.05$). There was no difference between the two groups in terms of the risk of other events. Compared to women without PH, in pregnant women with CHD and PH, the probability of pre-term delivery, low birth weight, and HF were much higher (all $P < 0.001$) (**Table 3**).

Compared to pregnant women with CHD whose cardiac functional class was NYHA I–II, pregnant women with CHD whose cardiac functional class was NYHA III–IV had significantly higher aORs for pre-term delivery, preeclampsia, cesarean section, fetal growth restriction, infant of low birth weight, PH, and respiratory/pulmonary diseases. Compared to women with NYHA functional class I–II, the probability of pre-term birth, low birth weight, preeclampsia, growth restriction, PH, and respiratory diseases were much higher than in women with NYHA functional class III–IV (**Table 4**).

For the pregnant women with CHD who underwent CHD surgery, the risk of pre-term delivery, low birth weight, HF, cesarean section, and pulmonary hypertension were significantly lower than in pregnant women with CHD who did not undergo CHD surgery. There were no differences between the two groups in terms of the probability of the other events. The incidence of pre-term delivery, HF, PH were much higher in women with CHD who did not undergo CHD surgery compared to those who did (**Supplementary Table 4**).

There was no difference in the probability of most events between severe CHD patients and mild-moderate CHD patients. However, for women with severe CHD, the probability of gestational diabetes and PH was significantly lower than in pregnant women with mild-to-moderate CHD. The probability of infants being low birth weight was significantly greater than in pregnant women with mild-to-moderate CHD (**Supplementary Table 5**).

A total of 128 (12.3%) patients with CHD were administered diuretics during pregnancy. Eighty-two patients (7.9%) took digoxin during pregnancy. Depending on the severity of PH, one or more targeted drugs to reduce PH were prescribed, including sildenafil, tadalafil, vantavir, remodulin, and even nitric oxide. According to cardiac function, drugs used included dopamine, dobutamine, epinephrine, norepinephrine, milrinone, pituitrin, and levosimendan. Extracorporeal membrane oxygenation was applied postoperatively in three patients (0.3%) because of PH and HF; despite this, all three patients died due to multiple organ failure. In our data, there were four patients with embolism events (0.4%), so the rate of corresponding administration of anticoagulant drugs was high.

Follow-Up

There were 739 mothers with CHD who underwent follow-up for 5.21 ± 2.63 years after discharge, and the follow-up rate was 71.06%. Twenty-eight (3.79%) patients had HF, 89 (12.04%) patients had arrhythmia, five (0.68%) patients died after discharge, 147 (19.89%) patients had PH, 36 (4.87%) patients had activity limitations, and 41 (5.55%) patients were still taking medication because of PH or cardiac dysfunction. In terms of offspring, four (0.54%) infants died and six (0.81%) infants had growth restrictions on account of premature birth and low birth weight. Fourteen (1.89%) infants were born with CHD. One (0.14%) infant had mental developmental

TABLE 2 | Adverse cardiovascular, obstetric, and fetal events experienced by women with and without CHD admitted for delivery.

	CHD (*n* = 1,040)	No CHD (*n* = 18,384)	*P* value	Crude OR (95%CI)	Adjusted *P* value	Adjusted OR (95%CI)
Obstetric events						
Hypertension in pregnancy	23 (2.21)	250 (1.36)	0.025	1.64 (1.07–2.53)	0.028	1.75 (1.05–2.50)
Placenta previa	24 (2.31)	557 (3.03)	0.185	0.76 (0.50–1.14)	0.170	0.89 (0.58–1.36)
Gestational diabetes	139 (13.37)	3166 (17.22)	0.006	0.74 (0.62–0.89)	0.002	0.76 (0.63–0.91)
Placental abruption	8 (0.77)	55 (0.30)	0.012	2.58 (1.23–5.44)	0.013	2.77 (1.28–5.96)
Hemorrhage	137 (13.17)	3124 (16.99)	0.001	0.74 (0.62–0.89)	0.001	0.79 (0.65–0.95)
Pre-term delivery	142 (13.65)	1234 (6.71)	<0.001	2.2 (1.82–2.65)	<0.001	1.77 (1.44–2.18)
Preeclampsia	68 (6.54)	980 (5.33)	0.094	1.24 (0.96–1.60)	0.088	1.05 (0.79–1.40)
Prolonged pregnancy	1 (0.10)	50 (0.27)	0.303	0.35 (0.05–2.56)	0.363	0.40 (0.06–2.92)
Cardiovascular events						
Heart failure	51 (4.90)	74 (0.40)	<0.001	12.76 (8.88–18.33)	<0.001	10.03 (6.51–15.47)
Arrhythmia	132 (12.69)	862 (4.69)	<0.001	2.96 (2.43–3.59)	<0.001	2.39 (1.94–2.96)
Thromboembolic event (stroke, PE, and so on)	4 (0.38)	42 (0.23)	0.319	1.69 (0.60–4.71)	0.318	1.87 (0.64–5.45)
Delivery procedure						
Cesarean section	821 (78.94)	9032 (49.24)	<0.001	3.90 (3.35–4.54)	<0.001	4.52 (3.87–5.21)
Artificial rupture of the membranes	26 (2.50)	767 (4.17)	0.009	0.59 (0.40–0.88)	0.008	0.51 (0.34–0.76)
Induction	26 (2.50)	750 (4.08)	0.012	0.60 (0.41–0.90)	0.013	0.54 (0.36–0.80)
Fetal events						
Fetal distress	4 (0.38)	2111 (11.48)	<0.001	0.03 (0.01–0.08)	<0.001	0.03 (0.01–0.08)
Fetal growth restriction	12 (1.15)	84 (0.46)	0.003	2.54 (1.38–4.67)	0.003	2.50 (1.35–4.66)
Fetal malformation	2 (0.19)	35 (0.19)	0.994	1.01 (0.24–4.21)	0.979	1.03 (0.25–4.35)
Fetal death or stillbirth	4 (0.38)	72 (0.39)	0.972	0.98 (0.36–2.69)	0.983	1.12 (0.41–3.09)
Infant of low-birth weight	89 (8.56)	802 (4.36)	<0.001	2.05 (1.63–2.58)	<0.001	1.84 (1.44–2.34)
Other events						
Pulmonary hypertension	271 (26.06)	99 (0.54)	<0.001	65.09 (51.14–82.84)	<0.001	57.95 (42.89–78.30)
Respiratory/pulmonary	14 (0.12)	103 (0.88)	0.004	2.42 (1.38–4.25)	0.002	2.47 (1.40–4.34)
Systemic hypertension	21 (2.02)	396 (2.15)	0.776	0.94 (0.60–1.46)	0.772	0.63 (0.38–1.05)
Hyperlipidemia	0 (0)	32 (0.17)	0.993	NC	0.990	NC
Mental health	1 (0.10)	23 (0.13)	0.801	0.77 (0.10–5.70)	0.808	0.78 (0.10–6.04)
Neurologic/CNS	1 (0.10)	24 (0.13)	0.762	0.74 (0.10–5.45)	0.779	0.99 (0.13–7.34)

CHD, congenital heart disease; CI, confidence interval; CNS, central nervous system; NC, not calculated; OR, odds ratio; PE, pulmonary embolism; Values are n (%) unless otherwise indicated.

delay due to chromosomal problems and lack of oxygen during birth. The other mothers and offspring were in good health.

In the control group, 740 mothers without CHD were followed up for 5.37 ± 2.52 years after discharge. One (0.14%) mother suffered HF, 32 (4.32%) mothers had arrhythmia, no mothers died after discharge, two (0.27%) mothers had PH, one (0.14%) mother had activity limitations, and one (0.14%) mother was still taking medication because of primary PH and cardiac dysfunction. In terms of the offspring, no infants died, one (0.14%) infant had growth restriction on account of premature birth and low birth weight, four (0.54%) infants were born with CHD, no infants had mental developmental delay, and the other mothers and offspring were in good health (**Figure 4**).

DISCUSSION

The major findings of our study were as follows. First, pregnant women with CHD had a longer hospital stay, more hospitalizations, higher costs, a higher mortality rate, and a higher probability of complications than pregnant women without CHD. Second, in the subgroup analysis, PH, decreased cardiac function, and no prior surgical treatment for CHD further increased the risk of complications in pregnant women

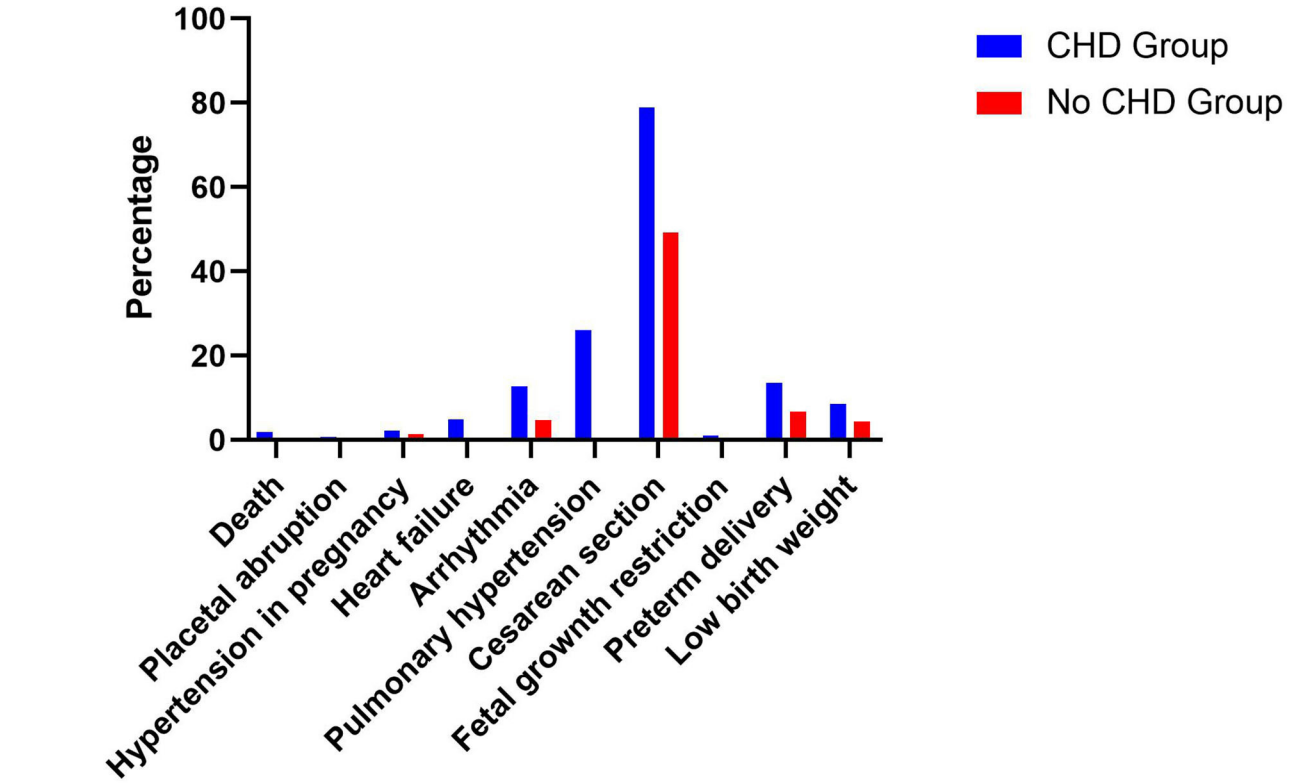

FIGURE 3 | Adverse events in pregnant women with and without CHD.

with CHD. Third, the fetuses of mothers with CHD were more likely to suffer complications than the fetuses of mothers without CHD. Fourth, the offspring of mothers with CHD seemed to be more likely to have CHD, facing growth restrictions and other problems from the beginning of life.

Pregnant women with CHD had significantly greater probability of several events and a higher death rate than women without CHD (1.92 vs. 0.02%; $P < 0.001$), and this finding is consistent with the findings of a previous study by Schlichting et al. (6). Our death rate was higher than that observed in Registry of Pregnancy and Cardiac Disease papers, and that is most likely because we included more women with CHD and severe PH or Eisenmenger Syndrome (7). Moreover, in the group without CHD, death was caused by amniotic fluid embolism, among other reasons. Moreover, although most of the women were healthy in the control group, some women did have other heart diseases, such as rheumatic heart disease and cardiomyopathy. This accounts for the surprisingly high PH rate (0.5%) in the control population, as well as the high arrhythmia rate.

For the pregnant women with CHD combined with PH, the probability of pre-term delivery, infant of low birth weight, and HF was much higher, which is consistent with previous studies suggesting that maternal mortality and morbidity rates remain high in women with PH related to CHD (8, 9). Among our 59 patients with Eisenmenger Syndrome, 10 (16.95%) died during hospitalization or were discharged from the hospital without medical instructions. Although some women with CHD do give birth to children, continuation of pregnancy is not recommended for pregnant women with Eisenmenger Syndrome in view of poor outcomes. During hospitalization, drugs used to treat PH included bosentan, sildenafil, alprostadil, iloprost, and alprostadil, and nitric oxide.

Pregnant women with CHD with NYHA functional class III–IV were at greater risk during pregnancy and had a longer hospital stay. Among these patients, eight died while in hospital or after being discharged. For women with HF, medications included dopamine, epinephrine, dobutamine, norepinephrine, milrinone, and pituitrin. Extracorporeal membrane oxygenation was also used.

We found marked differences in HF in pregnant women with unoperated CHD and pregnant women with operated CHD, and this finding was not consistent with the prior findings of Yadav et al. who reported excellent and comparable maternal and fetal outcomes in unoperated and operated CHS patients (10). Sliwa et al. reported similar findings (11). Although during our follow-up, some mothers with CHD still did not undergo surgery, we

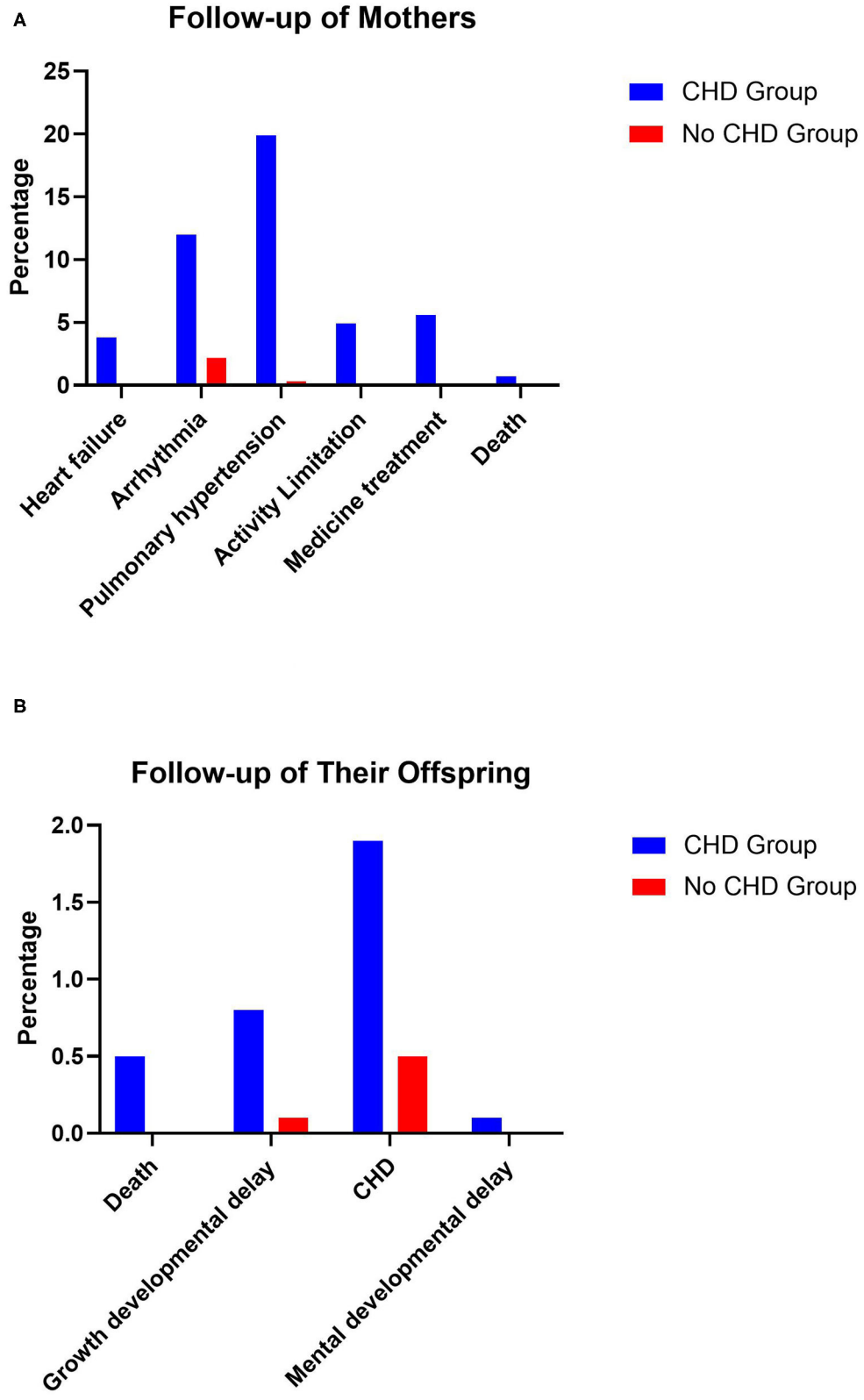

FIGURE 4 | Follow-up of the mothers and their offspring.

TABLE 3 | Adverse cardiovascular, obstetric, and fetal events experienced by women with CHD admitted for delivery by presence of PH.

	CHD with PH (*n* = 271)	CHD without PH (*n* = 769)	*P* value	Crude OR (95%CI)	Adjusted *P* value	Adjusted OR (95%CI)
Obstetric events						
Hypertension in pregnancy	7 (2.58)	16 (2.08)	0.629	1.25 (0.51–3.07)	0.724	1.19 (0.46–3.04)
Placenta previa	4 (1.48)	20 (2.60)	0.295	0.56 (0.19–1.66)	0.412	0.63 (0.21–1.89)
Gestational diabetes	27 (9.96)	112 (14.56)	0.057	0.65 (0.42–1.00)	0.123	0.70 (0.45–1.10)
Placental abruption	2 (0.74)	6 (0.78)	0.945	0.95 (0.19–4.71)	0.961	0.96 (0.18–5.00)
Hemorrhage	35 (12.92)	102 (13.26)	0.884	0.97 (0.64–1.46)	0.531	0.87 (0.57–1.34)
Pre-term delivery	95 (35.06)	77 (10.01)	<0.001	2.84 (1.97–4.09)	<0.001	2.23 (1.52–3.29)
preeclampsia	21 (7.75)	47 (6.11)	0.350	1.29 (0.76–2.20)	0.879	0.96 (0.53–1.71)
Cardiovascular events						
Heart failure	34 (12.55)	17 (2.1)	<0.001	6.35 (3.48–11.57)	<0.001	4.95 (2.48–9.87)
Arrhythmia	35 (12.92)	97 (12.61)	0.898	1.03 (0.68–1.55)	0.873	1.04 (0.68–1.58)
Thromboembolic event(stroke, PE, and so on)	1 (0.37)	3 (0.39)	0.961	0.95 (0.10–9.13)	0.919	1.12 (0.12–10.92)
Delivery procedure						
Cesarean section	240 (88.56)	581 (75.55)	<0.001	2.51 (1.67–3.77)	<0.001	2.32 (1.53–3.51)
Artificial rupture of the membranes	2 (0.74)	24 (3.12)	0.047	0.23 (0.05–0.98)	0.049	0.10 (0.01–0.77)
Induction	2 (0.74)	24 (3.12)	0.047	0.23 (0.05–0.98)	0.049	0.09 (0.01–0.72)
Fetal events						
Fetal distress	10 (3.69)	48 (6.24)	0.120	0.58 (0.29–1.15)	0.117	0.46 (0.21–1.02)
Fetal growth restriction	4 (1.48)	8 (1.04)	0.566	1.43 (0.43–4.77)	0.545	1.17 (0.32–4.31)
Fetal malformation	1 (0.37)	1 (0.13)	0.460	2.84 (0.18–45.63)	0.477	2.74 (0.17–43.93)
Infant of low-birth weight	91 (33.58)	48 (6.24)	<0.001	2.68 (1.72–4.17)	<0.001	2.40 (1.51–3.79)
Other events						
Respiratory/pulmonary diseases	7 (2.58)	7 (0.91)	0.049	2.89 (1.00–8.31)	0.048	2.94 (1.02–8.44)
Systemic hypertension	4 (1.48)	17 (2.21)	0.463	0.66 (0.22–1.99)	0.455	0.63 (0.20–2.12)

Values are n (%) unless otherwise indicated. Abbreviations as in ***Tables 1***, ***2***.

do recommend early surgical treatment for women with CHD before pregnancy.

In our study, severe CHD was more commonly cyanotic CHD with right to left shunt, such as tetralogy of Fallot, so PH rates were lower than that of patients with mild-to-moderate CHD. Our results suggest that the risk of the most adverse events during delivery was not significantly different in women with different CHD severities, and this may have been because the differences in risk were not fully established. This finding was not consistent with that of Avila et al. (12, 13) who argued that pregnancy in women with complex (severe) CHD was associated with high maternal and offspring risks.

Infants whose mothers had CHD were more likely to be delivered pre-term with a low birth weight, and this is similar to the findings of Takatsuki et al. (14). Moreover, these infants were more likely to experience a growth restriction due to the medications taken by women with CHD or the mothers' comorbidities, such as HF. Advances in fetal echocardiography have improved prenatal diagnosis of CHD and allowed better delivery and perinatal management (15, 16). It is also very important to monitor and follow pregnant women with CHD using echocardiography (17, 18).

During our follow-up, the vast majority of outcomes were good in pregnant women with CHD and their offspring. In addition to the maternal death in hospital, four mothers died after leaving hospital. Due to cardiac function, the daily activities in some pregnant women with PH are limited. The PH detected during pregnancy decreased after childbirth in a few women. The pregnant women with severe PH continued taking drugs such as bosentan and sildenafil. Cardiac function gradually recovered after childbirth in a few pregnant women who survived. The growth and development of some pre-term infants was slower than that of their peers; however, they gradually caught up. The offspring of mothers with CHD were at a higher risk of CHD than their peers, which was consistent with the view that CHD is caused by many factors including heredity and environment (19). Pre-term and low birth weight babies had worse outcomes, and three died after discharge, and these findings are consistent with that of Videbæk et al. (20).

Considering the above, the multidisciplinary management of these pregnant women by experts in the field of CHD is imperative, and a "pregnancy heart team" is needed (21, 22). Besides obstetricians and gynecologists, cardiologists, cardiac surgeons, cardiopulmonary bypass surgeons, pediatricians,

TABLE 4 | Adverse cardiovascular, obstetric, and fetal events experienced by women with CHD admitted for delivery by NYHA.

	CHD With NYHA III∼IV ($n = 122$)	CHD With NYHA I∼II ($n = 918$)	*P* value	Crude OR (95%CI)	Adjusted *P* value	Adjusted OR (95%CI)
Obstetric events						
Hypertension in pregnancy	3 (2.46)	20 (2.19)	0.843	1.13 (0.33–3.87)	0.747	1.23 (0.36–4.21)
Placenta previa	2 (1.64)	22 (2.40)	0.603	0.68 (0.16–2.92)	0.692	0.74 (0.17–3.22)
Gestational diabetes	10 (8.20)	129 (14.05)	0.078	0.55 (0.28–1.07)	0.110	0.58 (0.29–1.13)
Placental abruption	1 (0.82)	7 (0.76)	0.946	1.08 (0.13–8.82)	0.796	1.32 (0.16–11.10)
Hemorrhage	20 (16.39)	117 (12.75)	0.264	1.34 (0.8–2.25)	0.187	1.42 (0.84–2.39)
Pre-term delivery	58 (47.54)	84 (9.15)	<0.001	9.00 (5.91–13.70)	<0.001	8.69 (5.64–13.38)
preeclampsia	18 (14.75)	50 (5.45)	<0.001	3.01 (1.69–5.34)	<0.001	3.05 (1.71–5.46)
Cardiovascular events						
Arrhythmia	17 (13.93)	115 (12.53)	0.661	1.13 (0.65–1.96)	0.674	1.05 (0.59–1.88)
Thromboembolic event(stroke, PE, and so on)	0 (0)	4 (0.44)	NC	NC	NC	NC
Delivery procedure						
Cesarean section	116 (95.08)	705 (76.80)	<0.001	5.84 (2.54–13.46)	<0.001	4.03 (1.72–9.48)
Artificial rupture of the membranes	0 (0)	26 (2.83)	0.996	NC	0.996	NC
Induction	0 (0)	26 (2.83)	0.996	NC	0.996	NC
Fetal events						
Fetal distress	5 (4.10)	53 (5.77)	0.451	0.70 (0.27–1.78)	0.420	0.68 (0.26–1.75)
Fetal growth restriction	4 (3.28)	8 (0.87)	0.030	3.86 (1.14–13.00)	0.025	4.04 (1.19–13.67)
Fetal malformation	1 (0.82)	1 (0.11)	0.153	7.58 (0.47–121.95)	0.144	7.96 (0.49–128.27)
Fetal death or stillbirth	4 (3.28)	0 (0)	0.997	NC	0.997	NC
Infant of low-birth weight	30 (24.59)	59 (6.43)	<0.001	4.75 (2.91–7.74)	<0.001	3.66 (2.12–6.31)
Other events						
Pulmonary arterial hypertension	80 (65.57)	191 (20.80)	<0.001	7.25 (4.83–10.88)	<0.001	7.40 (4.87–11.24)
Respiratory/pulmonary	7 (5.74)	7 (0.76)	<0.001	7.92 (2.73–22.99)	<0.001	9.91 (2.88–34.14)
Systemic hypertension	4 (3.28)	17 (1.85)	0.299	1.80 (0.59–5.43)	0.289	2.66 (0.80–8.83)

Values are n (%) unless otherwise indicated. Abbreviations as in ***Tables 1–3****.*

anesthesiologists, surgical intensive care unit specialists, respiratory physicians, and other specialists, including clinical geneticists, social workers, and psychologists, should be involved (23, 24). Appropriate care is imperative (25, 26). Pre-pregnancy counseling must be performed by cardiologists with expertise in both CHD and pregnancy, with a detailed clinical assessment of the patient and the current hemodynamic situation, including echocardiography and an exercise test (27). The team should monitor all patients with moderate-to-severe CHD before pregnancy for timely counseling and advice during pregnancy in order to plan antenatal care, including delivery and post-partum follow-up and the need for cardiac monitoring. In our study, the treatment and care of some pregnant women with CHD was discussed by experts from multiple departments or even the whole hospital, resulting in good outcomes for critically ill women.

Considering the lack of data on oxygen saturation in some cases, there was no comparison of cyanotic and acyanotic CHD in our study. Overall, regardless of our findings, a few issues remain controversial and unclear. To understand the unique challenges this population presents, further study is necessary (28).

Study Strengths and Limitations

The strength of the current study was that it represents the largest case series analysis from a single institution to date and the treatment protocols were more consistent than that of multi-center studies.

In terms of limitations, our data involved patients mainly from the Beijing area, which may limit the generalizability of our results to other regions. This was a retrospective single-center study in which data were collected from medical records. We focused on the delivery period, as most patients were referred in the later stages of pregnancy, and we were often unable to obtain information on events occurring early during pregnancy, including miscarriages or planned interruption of pregnancies; therefore, the analysis may contain some bias. Meanwhile, some data were incomplete, incorrectly entered, or unavailable. Moreover, some follow-up information and the results provided by individual family members may not be accurate due to privacy concerns. CHD was diagnosed by echocardiography in some infants, whilst it was only determined using auscultation and clinical judgment in others, and this difference may have led to errors. Since the outbreak of 2019-nCoV, many women with CHD and their children have seldom visited the hospital, which led to some follow-up data being provided by telephone,

which may not be as accurate as data obtained during face-to-face consultations.

Conclusions

This study provides a very detailed analysis of pregnancy events in women with CHD based on PH subgroup, prior history of CHD surgery, NYHA class, and CHD severity level. PH and the decrease of cardiac function increase the perinatal risk in women with CHD, and CHD surgery before pregnancy is recommended for women with CHD. The differences in outcomes for women with severe and mild-to-moderate CHD needs further study. The majority of adult CHD patients tolerate pregnancy well, but women with CHD have higher risks. Pregnant women with CHD may require closer monitoring and management than healthy women. A multidisciplinary pregnancy heart team provides the best specialist care. Although the vast majority of women with CHD and their offspring were well during the follow-up period, the fetuses and newborns of these women were at higher risk of CHD, and women with CHD and their offspring were more likely to experience problems from immediately after birth.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Research Committee of Beijing An Zhen Hospital affiliated to Capital Medical University. Written informed consent was not required for this study, in accordance with the local legislation and institutional requirements.

AUTHOR CONTRIBUTIONS

YLiu: data collection, summarizing the data, data analysis, followup, and drafting and revising the article. YLi, JZ, WZ, and ZB: obstetrics and gynecology data analysis. XM, YZ, CZ, KL, QY, and LS: data statistics. YZ, YY, and JY: drawing. GL: supervised the study. XM and XF: revised the article. JW: plan the study, study design, and revised the article. All authors have read and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

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REVIEW
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Gestational Diabetes Mellitus and Preeclampsia: Correlation and Influencing Factors

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Gestational diabetes mellitus (GDM) and preeclampsia (PE) are common pregnancy complications with similar risk factors and pathophysiological changes. Evidence from previous studies suggests that the incidence of PE is significantly increased in women with GDM, but whether GDM is independently related to the occurrence of PE has remained controversial. GDM complicated by PE further increases perinatal adverse events with greater impact on the future maternal and offspring health. Identify factors associated with PE in women with GDM women, specifically those that are controllable, is important for improving pregnancy outcomes. This paper provides the findings of a review on the correlation between GDM and PE, factors associated with PE in women with GDM, possible mechanisms, and predictive markers. Most studies concluded that GDM is independently associated with PE in singleton pregnancy, and optimizing the treatment and management of GDM can reduce the incidence of PE, which is very helpful to improve pregnancy outcomes.

Keywords: gestational diabetes, preeclampsia, pregnancy, polycystic ovary syndrome, obesity

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INTRODUCTION

Gestational diabetes mellitus (GDM) and preeclampsia (PE) are common complications in pregnancy with similar risk factors, including obesity, advanced age, and multiple pregnancy (1, 2). Moreover, in both GDM and PE, the pathophysiological processes involve oxidative stress, pro-inflammatory factor release, vascular endothelial dysfunction (3, 4), which all increase the risk of future maternal diabetes and cardiovascular disease (5–8); thus, a correlation between GDM and PE may exist.

GDM is defined as glucose intolerance diagnosed for the first time during pregnancy (9). The International Association of Diabetes and Pregnancy Study Groups (IADPSG) recently updated the diagnostic criteria for GDM according to the findings of the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study, an oral glucose tolerance test (OGTT) must be performed in a fasting state using 75 g of glucose at 24–28 weeks (10). In 2013, the World Health Organization (WHO) further defined the diagnostic criteria of GDM. GDM is defined as meeting the above 75 g OGTT diagnostic criteria at any time during pregnancy, and the upper limit levels of fasting and 2-h blood glucose were defined (11). With the increasing prevalence of obesity and changes in people's lifestyle, the prevalence of GDM has also significantly increased two to three times in ∼10 years (12–14). The prevalence rate of GDM in the Middle East and some North African countries has reached 15.2% (2), while that of Chinese mainland is 14.8% (15). Increased insulin resistance and pancreatic

β-cell dysfunction are the major pathogenesis of GDM, which may already exist before pregnancy, especially in obese populations (2). GDM is associated with adverse pregnancy outcomes. Studies have found that the incidence of PE is significantly increased in GDM (16, 17). However, whether GDM is independently associated with the occurrence of PE or because of the effects of their common risk factors, especially obesity, remains controversial.

PE refers to new hypertension (systolic or diastolic blood pressure ≥140 or ≥90 mmHg, respectively) diagnosed at or after 20 weeks of gestation with proteinuria, or at least one other organ (kidney, liver, nervous system, blood system, and uteroplacenta) dysfunction (18). PE is the main cause of maternal and fetal mortality and morbidity (19, 20). GDM complicated by PE further increases perinatal adverse events (21–24), future maternal risk of chronic hypertension, cardiovascular disease, and diabetes (25–27); offspring body mass index (BMI) also steadily increases over time (28). Identifying factors associated with occurrence of PE in women with GDM, especially those that are controllable, is important for improving pregnancy outcomes. This review describes the relationship between GDM and PE, factors associated with occurrence of PE in women with GDM, and impact of GDM on PE in twin pregnancy and in pregnant women with polycystic ovary syndrome (PCOS). It also explores possible impact mechanisms and predictive markers to improve pregnancy outcomes.

SEARCH STRATEGY AND SELECTION CRITERIA

We retrieved studies from the PubMed, Ovid, and Wiley from the inception of the databases to June 2021, with the search terms "gestational diabetes mellitus" and "preeclampsia." We cross-referenced these terms with "obesity," "body mass index," "gestational weight gain," "early onset," "blood glucose," "polycystic ovary syndrome," "twin pregnancy," "management," "mechanism," "predictive markers," "risk factors," "insulin," "metformin," "Glibenclamide." We carefully screened all the articles, and focused on articles covering multivariate analysis to judge the independent correlation.

CORRELATION BETWEEN GDM AND PE

HAPO is a large international prospective blinded cohort study involving 23,316 pregnant women in 15 centers from nine countries, assessing the relationship between blood glucose below diabetes levels and pregnancy outcomes. The HAPO study found that the occurrence of PE is positively associated with blood glucose level even after adjusting for clinical center, age, BMI, height, smoking status, alcohol consumption, family history of diabetes, gestational age at OGTT, and urinary tract infection (29). Following the IADPSG diagnostic criteria, secondary analysis showed that non-obese women with GDM was also associated with PE after adjusting for the above confounding factors, but the association was lower than obesity (16). Population-based retrospective cohort studies in several countries also showed GDM was independently associated with the occurrence of PE (17, 30–40). According to a retrospective cohort study in Sweden, obesity is the main confounding factor (32); however, another retrospective cohort study in France suggested that obesity is not related with the occurrence of PE in women with GDM (36). Different diagnostic criteria for GDM have had little impact on the occurrence of PE (41). A few studies suggest that GDM is not associated with the occurrence of PE after removing the effect of pre pregnancy BMI and other factors (42–46). A retrospective cohort study in Germany showed that there was no independent correlation between GDM and PE, regardless of obesity before pregnancy, and it was unknown whether it was related to the strict control of blood glucose levels (45). In studies conducted in Australia and Japan (42, 43), cases included those within the diagnostic criteria of IADPSG but not up to their own national standards, so blood glucose levels were relatively low, which may have affect the results. Based on these previous findings (**Table 1**), most studies support that GDM was independently associated with the occurrence of PE in singleton pregnancy. In addition, GDM is also a major risk factor for recurrent (47) and new postnatal PE in the absence of a PE history (48). The history of GDM in first pregnancy is also a risk factor for PE in the second pregnancy (49).

PE also affects the occurrence of GDM; a retrospective cohort study in Korea showed that a history of PE in first pregnancy is a risk factor for the development of GDM in subsequent pregnancies (50). However, a retrospective study in Chile suggested that the history of PE in previous pregnancies is negatively associated with the occurrence of GDM in the next pregnancy (13). Whether PE associated with the occurrence of GDM should be further confirmed in large sample studies.

FACTORS ASSOCIATED WITH OCCURRENCE OF PE IN WOMEN WITH GDM

Pre Pregnancy BMI

BMI is a common index used to evaluate nutritional status, even among pregnant women. The World Health Organization (WHO) categorizes BMI into underweight, normal weight, overweight, and obesity with values <18.50, 18.50–24.99, 25.00–29.99, and ≥30.00 kg/m^2, respectively (51). Obesity is a common risk factor for GDM and PE, an individual participant data meta-analysis of European, North American and Australian cohorts showed that obesity increased the risk of GDM by three times and the risk of PE by two times (52). Both obesity and GDM are independent associated with PE (16, 31, 32), and the combination of the two has a greater impact than either one

Abbreviations: AGEs, advanced glycation end products; BMI, body mass index; CRP, C-reactive protein; GDM, gestational diabetes mellitus; GWG, gestational weight gain; HAPO, Hyperglycemia and Adverse Pregnancy Outcome; HbA1c, glycosylated hemoglobin; IADPSG, International Association of Diabetes and Pregnancy Study Groups; IL-6, interleukin-6; IOM, Institute of Medicine; NAM, National Academy of Medicine; NETs, sneutrophil extracellular traps; NO, nitric oxide; OGTT, oral glucose tolerance test; PCOS, polycystic ovary syndrome; PE, preeclampsia; PlGF, placental growth factor; sFlt1, soluble fms-like tyrosine kinase-1; TNF-α, tumor necrosis factor; WHO, World Health Organization.

TABLE 1 | The independent association of gestational diabetes mellitus with preeclampsia.

Country	References	Study period	Type of birth	Study design	GDM criteria	Number of GDM /No GDM	PE% GDM /No GDM	Study content	Result
Nine countries	Catalano et al. (16)	2000–2006	Single	PC	IADPSG	2,518/16,238	5.9/3.5	Association	Positive
Australia	Stone et al. (37)	1996	Single	RC	NR	2,169/58,231	8.1/5.2	Association	Positive
	Cheung et al. (42)	2014–2016	Single	RC	IADPSG	375/4,873	4.0/2.0	Association	Negative
Brazil	Schmidt et al. (41)	1991–1995	All	PC	ADA2000(75g OGTT)/	Total 4,572	NR	Association	Positive
					WHO1999			Association	Positive
Canada	Nerenberg et al. (34)	2000–2009	All	RC	CDA	15,404/407,268	2.6/1.2	Association	Positive
	Lai et al. (40)	2005–2011	Single	RC	CDA	18,137/306,576	3.4/1.7	Association	Positive
	Hiersch et al. (35)	2012–2016	Single	RC	CDA	16,731/250,211	1.1/0.7	Association	Positive
Denmark	Ovesen et al. (30)	2004–2010	Single	RC	ICD-10 O24.4	9,014/389,606	8.2/3.9	Association	Positive
France	Cosson et al. (36)	2002–2010	Single	RC	French criteria/WHO1985	2,097/13,436	3.1/2.0	Association	Positive
	Billionnet et al. (39)	2012	All	RC	IADPSG	57,629/735,519	2.6/1.6	Association	Positive
Germany	Weschenfelder et al. (45)	2012–2016	Single	RC	IADPSG/WHO2013	614/5,175	6.8/2.7	Association	Negative
Israel	Košir Pogačnik et al. (46)	2002–1026	Single	RC	NDDG /IADPSG	10,248/226,676	2.1/1.8	Association	Negative
Japan	Shindo et al. (43)	2000–2009	Single	RC	IADPSG	503/2,789	2.0/1.8	Association	Negative
Sweden	Ostlund et al. (32)	1992–1996	Single	RC	ICD-9 648W	3,448/427,404	6.1/2.8	Association	Positive
	Fadl et al. (33)	1991–2003	Single	RC	ICD-9/ICD-10	10,525/1,249,772	5.9/2.6	Association	Positive
	Hilden et al. (31)	1998–2012	Single	RC	ICD-10 O24.4	13,057/1,252,093	3.4/1.8	Association	Positive
Uruguay	Conde-Agudelo et al. (17)	1985–1997	All	RC	ICD-10 O24.4	5,309/873,371	17.2/4.9	Association	Positive
USA	Joffe et al. (44)	1995	Single	PC	NDDG	81/3,381	12.4/7.7	Association	Negative
	Bryson et al. (38)	1992–1998	All	CC	ICD-9 648.8	Total 62,982	NR	Association	Positive

ADA, American Diabetes Association; CC, case-control; CDA, Canadian Diabetes Association; GDM, gestational diabetes mellitus; IADPSG, International Association of Diabetes and Pregnancy Study Groups; ICD, International Classification of Diseases; NDDG, National Diabetes Data Group; NR, not reported; OGTT, oral glucose tolerance test; PC, prospective cohort; PE, preeclampsia; RC, retrospective cohort; WHO, World Health Organization.

alone (16, 31). A Sweden population-based retrospective cohort study that included the data of 13,057 women with GDM who needed treatment, analyzed the impact of pre pregnancy BMI on PE, and showed the highest risk of GDM with obesity, but without significant interaction between obesity and GDM. In addition, obesity had less effect on PE in women with GDM comparing with women without GDM, which may be the result of insulin resistance in both GDM and obesity (31). Most studies suggested that pre pregnancy BMI was independently associated with the occurrence of PE in women with GDM (23, 53–56). In a retrospective cohort study, maternal obesity, early GDM diagnosis and poor glycemic control were the three independent factors related to PE in women with GDM, of which obesity was the highest risk (56). Only one population-based retrospective study in France suggested that the incidence of PE in women with GDM was not associated with pre pregnancy BMI (36). In a randomized controlled trial evaluating metformin for GDM, obesity was not associated with PE in metformin- and/or insulin-treated women, but the incidence of PE was significantly associated with being overweight. The reason for this result may be related to the drug treatment and blood glucose control; furthermore, aspirin was not excluded as a confounding factor (57). In a prospective observational study, considering the level of blood glucose control and treatment methods, obesity was only related to PE in insulin treatment group with poor blood glucose control, but not in diet treatment group (regardless of blood glucose control) and insulin treatment group with good blood glucose control (58). Thus, the effect of pre pregnancy BMI on PE in women with GDM may be also related to blood glucose level and treatment methods.

Gestational Weight Gain (GWG)

GWG, another commonly used indicator for nutritional status during pregnancy, is related to pregnancy complications (59, 60). In 2009, the Institute of Medicine (IOM)/National Academy of Medicine (NAM) recommended that the total weight gain during pregnancy of underweight, normal weight, overweight, and obese women according to the WHO BMI classification should respectively be 12.5–18.0, 11.5–16.0, 7.0–11.5, and 5.0–9.0 kg. The average weekly weight gain in the middle and third stages of gestation should be 0.51 (0.44–0.58), 0.42 (0.35–0.50), 0.28 (0.23–0.33), and 0.22 (0.17–0.27) kg, respectively (61). A meta-analysis reported that 30, 34, and, 37% of women with GDM had insufficient, adequate, and excessive GWG (which occurred more in pre pregnancy overweight or obese women), respectively (62). Although GWG is significantly elevated in women with GDM combined with PE (23, 53), most studies considered that the overall excess GWG had no independent correlation with the occurrence of PE (23, 36, 53, 63–65); the same result was reported for obese women with GDM (66). A

recent retrospective cohort study of 1,606 women with GDM in China reported different conclusions, after adjusting for maternal age, pre pregnancy BMI, maternal education, *in vitro* fertilization, fasting, and 2 h glucose, the risk of the total excess GWG developing to PE is 2.06 times; with 2.28 and 2.17 times in the second and third trimesters, respectively (67). It has also been suggested that weight gain in early pregnancy is associated with the occurrence of PE (57). Since we were unable to determine whether pregnant women would develop GDM at the beginning of pregnancy, the management of weight after GDM diagnosis was more significant. A retrospective cohort study conducted in the US evaluated the effect of GWG on pregnancy outcome after the diagnosis of GDM; however, GWG after the diagnosis of GDM was not related to the occurrence of PE adjusted for black, pre pregnancy BMI, and chronic hypertension. However, in a logistic regression model, the weekly weight gain of pregnant patients after GDM diagnosis was evaluated as a continuous variable, after adjusting the pre pregnancy BMI, mother's age, and weekly weight gain before GDM diagnosis, the probability of PE increased by 83% for every 0.45 kg/week of weight gain (68). Recent prospective cohort study in China suggested that a unit increase in GWG level after GDM diagnosis is not related with the occurrence of PE, but in women with excessive GWG before GDM diagnosis, both adequate and excessive GWG after GDM diagnosis increased the incidence of PE (69). Both insufficient weight gain after diagnosis of GDM and total insufficient GWG are not associated with the occurrence of PE (36, 65, 67–69); however, in obese women with GDM, total insufficient GWG is negatively associated with the occurrence of PE (66). A meta-analysis of GWG and GDM pregnancy outcomes showed that excessive GWG is associated with an increased risk of pregnancy-induced hypertension, but PE was not analyzed separately (62). Further clinical studies are required to evaluate whether GWG affects PE occurrence in women with GDM, especially after the diagnosis of GDM. Furthermore, whether the recommended GWG criteria by the IOM /NAM in 2009 is applicable to women with GDM also requires further validation. A Chinese study found that among women with GDM, with weight gain within the receiver operating characteristic target, the incidence of pregnancy-induced hypertension is lower than that of women with weight gain within the IOM target (70). In an Australian study, for the GWG of women with GDM, 2 kg was subtracted from that of the IOM target, which did not improve the prognostic outcome (71).

GWG not only affects the occurrence of PE in women with GDM, but also perinatal outcomes in those complicated by PE. Although total excessive GWG is a protective factor for preterm birth, middle trimester excessive GWG is a risk factor for large gestational age and late trimester excessive GWG is a risk factor for severe PE and cesarean section (72). In conclusion, although GWG has no greater impact than pre pregnancy BMI on PE in women with GDM, it is a controllable factor during pregnancy.

Time of GDM Occurrence

There is no consensus on the screening and diagnosis of GDM in early pregnancy. Screening is usually recommended in the first trimester or during prenatal care to exclude the presence of diabetes in high-risk women (10, 11, 73). Opinions also differ on whether early- or later-onset GDM affects PE. This may be related to the heterogeneity in diagnostic criteria for early-onset GDM and different time definitions and sample sizes. A large retrospective cohort study in Portugal including 18,518 pregnant women with GDM reported that the incidence of early-onset GDM ($\leq$12 weeks) was 34.4% according to the IADPSG diagnostic criteria; there was no difference in the incidence of PE between women with early- and later-onset GDM (74). Furthermore, several studies have reported the same conclusion (55, 75–79). In early-onset GDM, metformin or insulin treatment is more needed (75, 78, 79), it is uncertain whether it will affect the occurrence of PE. However, women with early-onset GDM have more risk factors for PE, such as older age, multiple pregnancy, and higher pre pregnancy BMI (80, 81). Others suggest a significantly increased incidence of PE in women with early-onset GDM (81–84). A retrospective US cohort study of 2,596 diet-treated women with GDM shows a 2-fold incidence of PE in early diagnosis (<24 weeks) compared to women with GDM diagnosed after 24 weeks; the risk was 2.4-fold even after adjusting for maternal age, race, parity, weight, and glycemic control differences (82). In another prospective cohort study evaluating the risk of PE in women with GDM, the risk of PE in GDM diagnosed within 20 weeks of pregnancy was 8-fold, even after adjusting for pre pregnancy BMI, OGTT and control blood glucose levels (56). Whether early- or later- onset GDM affects the occurrence of PE needs to be verified by large sample prospective trials. However, for the high-risk population with GDM, early screening and active treatment may reduce the risk of PE (85, 86).

Blood Glucose

The HAPO study showed that PE is linearly positively associated with the maternal glucose level, for every 1-standard deviation increase in OGTT blood glucose (fasting, 1 h, and 2 h), with the odds ratio of PE between 1.21 and 1.28 (29). The 5th International Symposium on Gestational Diabetes recommended that the blood glucose control criteria during pregnancy for fasting, 1 h, and 2 h blood glucose levels be <5.3, <7.8, or <6.7 mmol/L, respectively (87). The risk of PE in women with GDM increases with increasing levels of glucose impairment at diagnosis (88, 89). However, optimizing glycemic treatment can reduce the occurrence of PE (23, 90, 91), and poor glycemic control is related to the occurrence of PE (54, 56–58). Whether the blood glucose level at OGTT or the blood glucose control level can independently predict the occurrence of PE is unclear. As previously reported, blood glucose control is an independent risk factor for PE (56, 57), and OGTT blood glucose levels are not associated with the occurrence of PE (56, 57, 92). However, others reported that although optimizing blood glucose treatment can reduce the risk of PE, it is not an independent influencing factor, but the OGTT fasting blood glucose level is independent and significantly correlated with the occurrence of PE (23). Accordingly, two other studies also support the finding that OGTT blood glucose levels are an independent risk factor for the development of PE (93, 94). A Chinese retrospective cohort study reported that the blood glucose level at OGTT and after

treatment of GDM did not independently predict the occurrence of PE, while the fasting blood glucose level at OGTT is an important risk factor for such (54). In conclusion, blood glucose levels should be more strictly controlled in women with severely-impaired glucose tolerance. Some prospective cohort studies and meta-analysis showed that glycosylated hemoglobin (HbA1c) ≥ 5.9% in early pregnancy significantly was associated with the risk of PE (95–98). It is controversial whether HbA1c level in the second trimester of pregnancy is related to the occurrence of PE, the secondary analysis of HAPO and a retrospective study showed that the HbA1c level during OGTT was related to the occurrence of PE (99, 100). However, two retrospective studies showed that HbA1c level in the second trimester of pregnancy was not associated with PE (54, 101). A higher HbA1c level (5.5–5.9%) within the normal range during OGTT also is an independent risk factor for preeclampsia in women with GDM in a China retrospective cohort study (102). The risk of PE in women with GDM is also related to blood glucose variability. Women with poor blood glucose monitoring compliance are more susceptible to PE than women with good compliance (103). Continuous blood glucose monitoring is helpful for detecting all postprandial blood glucose peaks and recording the impact of diet. It is conducive for the timely adjustment of the treatment plan and for reducing blood glucose variations. The incidence of PE is significantly lower than that in women whose blood glucose alone is monitored, and the mean amplitude of glycemic excursions is also an independent risk factor for PE (104). Blood glucose variability may affect the occurrence of PE by increasing oxidative stress. However, a prospective study with a small sample size showed that the glycemic variability in the third trimester of non-insulin dependent GDM was not associated with the incidence of PE (105).

Age, Parity, and Ethnicity

Age, parity and race are uncontrollable factors, which are also related to the occurrence of PE in GDM women. More studies suggested that advanced age was not independent associated the occurrence with PE in women with GDM (23, 54, 55). Only a retrospective study considered that advanced age was an independent risk factor for PE in women with GDM (53). In a randomized controlled trial, nulliparity was independently associated with the occurrence of PE in women with GDM (57), another retrospective study reached the same conclusion (53). Other studies showed that parity was not associated with PE in women with GDM (23, 54, 55). Ethnicity also has an impact on the occurrence of PE in women with GDM. In a randomized controlled trial in New Zealand/Australia, 724 multi-ethnic subjects were included, the risk of PE in Polynesian is twice that in European/Caucasian/mixed (57). In the retrospective study in US, there was no difference in the incidence of PE among different ethnicity, including Mexican American, Caucasian and African American (53). The same conclusion was reached in the retrospective study of Fiji, that is ethnicity had no effect on the occurrence of PE in women with GDM (55).

Table 2 summarizes whether the above factors are independently associated with the occurrence of PE in women with GDM.

Effect of GDM Treatment

The first treatment of GDM is lifestyle intervention, including diet and daily activities. When hyperglycemia is evident after ≥1–2 weeks of lifestyle interventions, daily glucose testing should be continued, and pharmacological treatment should be initiated. Insulin is the most traditionally-preferred drug; oral hypoglycemic drugs, glibenclamide and metformin, are also used in some countries (2). Considering that these drugs can cross the placenta, the American Diabetes Association does not recommend them as first-line drugs for GDM (106). Two randomized controlled trials showed that intervention with GDM (including dietary recommendations, blood glucose monitoring, and insulin treatment) significantly reduced the risk of PE (90, 91), and a meta-analyses revealed similar conclusions (107).

Lifestyle Intervention

Lifestyle intervention mainly includes diet and exercise, the diet should contain sufficient macronutrients and micronutrients, carbohydrates with low glycemic index are recommended (2). A randomized controlled trial showed that a Mediterranean Diet, supplemented with extra-virgin olive oil and pistachios, can reduce the incidence of adverse pregnancy events of GDM, the incidence of PE in women with GDM was not different from that without GDM (108). However, omega-3 fatty acids supplementation had no effect on the incidence of PE in women with GDM (109). Inositol is considered as a food supplement, randomized controlled trials and meta-analysis believe that it can prevent the occurrence of GDM, but it cannot prevent the occurrence of pregnancy induced hypertension in high-risk groups of GDM (110–112). For women diagnosed with GDM, inositol supplementation also cannot reduce the risk of pregnancy induced hypertension/PE (113–115). Meta-analysis showed that there was a significant negative association between smoking during pregnancy and incidence of PE (116), but smoking during pregnancy did not reduce the incidence of PE in women with GDM in a retrospective cohort study (117). Moderate exercises during pregnancy are helpful to control pregnancy weight and blood glucose for women with GDM, but it has no effect on the occurrence of PE (118, 119).

Insulin

Although women with GDM who require insulin treatment tend to have higher blood glucose at OGTT (120–122), there was no significant difference in the incidence of PE compared to that in women on diet treatment alone (23, 39, 120–122). This may be related to the better management in the insulin treatment group (121); even the incidence of PE in women with GDM treated with insulin is consistent with those with normal glucose tolerance (123). If insulin treatment reaches the established blood glucose control level, the risk of PE in GDM with obesity is not different from that in normal weight (58).

Glibenclamide

For the use of glibenclamide and insulin in GDM, more comparisons were reported on blood glucose control and neonatal outcomes, and less on PE. A retrospective cohort

TABLE 2 | Factors independent affecting the incidence of preeclampsia in women with gestational diabetes mellitus.

References	Country	Study design	Number of GDM	BMI	eGWG	iGWG	Early GDM	OGTT level	Glucose control	Age	Parity	Ethnicity
Yogev et al. (23)	USA	RC	1,813	Y	N			Y	N	N	N	
Cosson et al. (36)	France	RC	2,097	N	N	N						
Yogev et al. (53)	USA	RC	1,664	Y	N					Y	Y	N
Sun et al. (54)	China	RC	779	Y				N	N	N	N	
Osuagwu et al. (55)	Fiji	RC	255	Y			N			N	N	N
Phaloprakarn et al. (56)	Thailand	PC	813	Y			Y	N	Y			
Rowan et al. (57)	New Zealand / Australian	RCT	724	Y	Y			N	Y		Y	Y
Egan et al. (63)	Ireland	PC	543		N							
Kase et al. (64)	USA	RC	90		N							
Xie et al. (65)	Spain	RC	2,700		N	N						
Lima Ferreira et al. (66)	Portugal	PC	4,563		N	Y						
Shi et al. (67)	China	RC	1,606		Y	N						
Harper et al. (68)	USA	RC	635		Y	N						
Zheng et al. (69)	China	PC	3,126		Y	N						
Hosseini et al. (77)	Iran	PC	171				N					
Immanuel et al. (79)	New Zealand	RC	1,573				N					
Hawkins et al. (82)	USA	RC	2,596				Y					
Kalok et al. (93)	Malaysia	RC	1,105					Y				
Barden et al. (94)	Australia	PC	184					Y				

BMI, body mass index; eGWG, excessive gestational weight gain; GDM, gestational diabetes mellitus; iGWG, insufficient gestational weight gain; N, no; OGTT, oral glucose tolerance test; PC, prospective cohort; RC, retrospective cohort; RCT, randomized controlled trial; Y, yes.

study in California showed that the incidence of PE in a glibenclamide-treated group was twice that in an insulin-treated group, and the risk was still 2.32 times higher after adjusting for confounding factors (124). Another randomized controlled trial study found that there was no difference in the incidence of PE between glibenclamide- and insulin-treated groups (125). The same result was found even among women with GDM with significantly increased oral glucose stimulation test and fasting hyperglycemia (126).

Metformin

A randomized controlled trial of 733 pregnant women in 10 hospitals in New Zealand and Australia compared the pregnancy outcomes between the administration of metformin and insulin for GDM. Although the incidence of PE in the metformin-treated group was lower than that in the insulin-treated group, the difference was not statistically significant (127). In other studies, metformin also had no effect on the incidence of PE (128–131). However, the metformin-treated group had less weight gain after treatment (127, 129). No relevant data exist on whether metformin is advantageous in obese women with GDM. A recent meta-analysis evaluated the efficacy of metformin, glibenclamide, and insulin in the treatment of GDM. Metformin showed a trend of reducing PE compared with insulin, but there was no significant difference. The incidence of PE in the glibenclamide-treated group was slightly higher than that in insulin-treated group; however, there was also no significant difference (132). Metformin may prevent PE by reducing the production of anti angiogenic factors, improving endothelial dysfunction and changing cell homeostasis and energy allocation (133), it is expected to become an ideal drug for preventing PE in women with GDM.

EFFECT OF GDM ON THE OCCURRENCE OF PE IN TWIN PREGNANCY AND IN PREGNANT WOMEN WITH PCOS

Twin Pregnancy

With the increase in maternal age and application of assisted reproductive technology, the incidence of twin pregnancy has been increasing (134, 135). Twin pregnancy is a common risk factor of GDM and PE (1, 2), the correlation between twin pregnancy and hypertensive disease/PE was higher than that of GDM (34, 136). Population-based retrospective cohort studies across different time periods (2005–2011 and 2012–2016) in Canadians show a higher incidence of PE in twin pregnancies than in singletons, with or without GDM (35, 40). Retrospective case control studies in China and Australia also show a significantly higher incidence of PE in women with GDM with twin pregnancies than that in women with singletons (137, 138). The two population-based cohort studies in Canadians derived different conclusions on whether GDM is associated with PE in twin pregnancy. Early studies show that the risk

of PE in twin pregnancy women with GDM is still 1.54-fold after adjusting for maternal age, ethnicity, parity, and prior hypertension (40). However, recent studies suggest that GDM was not associated with PE in twin pregnancy after adjusting for maternal age, smoking, parity, race, pre pregnancy BMI, and auxiliary factors (35). This difference may be related to the fact that early studies did not adjust for pre pregnancy BMI, because obesity significantly increases the risk of PE (52). The conclusions of other studies revealed inconsistencies; some suggested that the incidence of PE in twin pregnant women with GDM was significantly higher than that without GDM (135, 138, 139), and GDM was independent associated with PE in twin pregnancy (135, 139), while others suggested no significant difference between the two groups (140, 141). Whether GDM is independent associated with PE in twin pregnancy requires further validation; overall, GDM has less impact on PE in twin pregnancy than in singleton pregnancy (35, 40, 135).

PCOS

Women with PCOS have increased insulin resistance and hyperandrogenemia (142, 143). PCOS increases the incidence of GDM and PE, and the results are independent of obesity and assisted reproductive technology (144–146). A meta-analysis showed that pregnant women with PCOS had a 2.89- and 1.87-fold risk of GDM and PE, respectively (145). The incidence of PE is significantly higher in women with GDM combined with PCOS than in those without PCOS (147–150). The risk was 2-3-fold after adjusting for factors such as age, pre pregnancy BMI, and parity (148–150). Only one study believes that there was no correlation between PCOS and PE in women with GDM after adjusting for confounding factors (147). A Chinese prospective study found no difference in the incidence of PE between women with GDM with PCOS and those without PCOS, although the result was affected by factors such as small sample size and early intervention (151). Pregnant women with PCOS combined with GDM tend to be older and have higher pre pregnancy BMI (152–154). It is necessary to determine whether GDM associated with PE in pregnant women with PCOS. A prospective, double-blind, multicenter trial including 228 pregnant women with PCOS in Norway revealed that there was no statistical correlation between early GDM and PE occurrence (152). Similarly, two other studies were added to the earlier one, which increased the number of pregnant women with PCOS to 722. The results still show that GDM did not increase the incidence of PE in pregnant women with PCOS, regardless of whether GDM occurred early or later (153). Another prospective study in China found that the incidence of PE in PCOS pregnant women with GDM is significantly higher than that in pregnant women without GDM but did not analyze whether it was independent associated with PE (154). Thus, the effect of GDM on PE in pregnant women with PCOS is less than the effect of PCOS on PE in women with GDM.

MECHANISM AND PREDICTIVE MARKERS

Although GDM is associated with PE, the exact mechanism underlying the two disease associations is unclear. The pathophysiological process of PE involves two stages, early insufficient trophoblast invasion leads to incomplete spiral artery remodeling, which causes placental ischaemia and oxidative stress. The diseased placenta progressively secretes elevated amounts of anti-angiogenic factors [soluble fms-like tyrosine kinase-1 (sFlt1) and soluble endoglin] that cause maternal inflammation and vascular endothelial dysfunction, and finally lead to systemic diseases (1, 155). Hyperglycemia can induce trophoblast inflammation and autophagy, inhibit trophoblast migration and invasion (156–158). Neutrophils in GDM are over-activated and release excessive neutrophil extracellular traps (NETs) (159, 160). Excessive NETs hinder the blood circulation in the villous space, resulting in placental ischemia, which is related to the occurrence of PE (161–163). Oxidative stress increases in women with GDM (164–166), hyperglycemia can induce oxidative stress through a variety of ways, including the formation of advanced glycation end products (AGEs) (166). The production of reactive oxygen species increases during oxidative stress, resulting in a decrease in circulating nitric oxide (NO) level and bioavailability (166), which leads to vasodilation dysfunction. AGEs are significantly increased in women with GDM (167), and can promote the occurrence of PE by inducing oxidative stress and inflammation (168–170). Moreover, the pro-inflammatory cytokines serum tumor necrosis factor-α(TNF-α) and Interleukin-6 (IL-6) have been found increased in the circulation of women with GDM (171, 172), which are associated with endothelial dysfunction (172), and also increased in women with PE (173, 174). Some studies suggest that TNF-α, IL-6, and C-reactive protein (CRP) are independent risk factors for PE in women with GDM (94, 175, 176), and others suggest that in addition to the increased level of CRP, the imbalance of Interleukin-17 /Interleukin-35 may also be involved in the pathogenesis of GDM complicated with PE (177). Genetic variants are also associated with PE in women with GDM, the MIR146Ars2910164CC genotype, HNF1αgene p. I27L TT genotype, and ACE I / D polymorphism DD genotype was significantly higher in women with GDM complicated with PE (178–180). Obesity is the main influencing factor of PE in women with GDM in this paper. There are many of same pathophysiological changes between obesity and GDM, but obesity was concluded to be associated with greater oxidative stress and inflammation including the imbalance of fat factors (181), which are related to the occurrence of PE. Hyperinsulinemia and insulin resistance caused by obesity before pregnancy are related to the migration of cytotrophoblast and the reduction of uterine spiral artery remodeling, which is more likely to lead to placental ischemia (182). The mechanism of gestational diabetes mellitus affecting the occurrence of preeclampsia is shown in **Figure 1**.

Multiple biochemical markers have been studied to predict the occurrence of GDM and PE, and CRP, TNF-α, IL-6, and B-type natriuretic peptides are common predictive markers (183, 184), but none are used as practical clinical markers. Serum sFlt1 / placental growth factor (PlGF) is a valid marker for predicting and diagnosing PE (185). It is also significantly elevated in the blood of women with

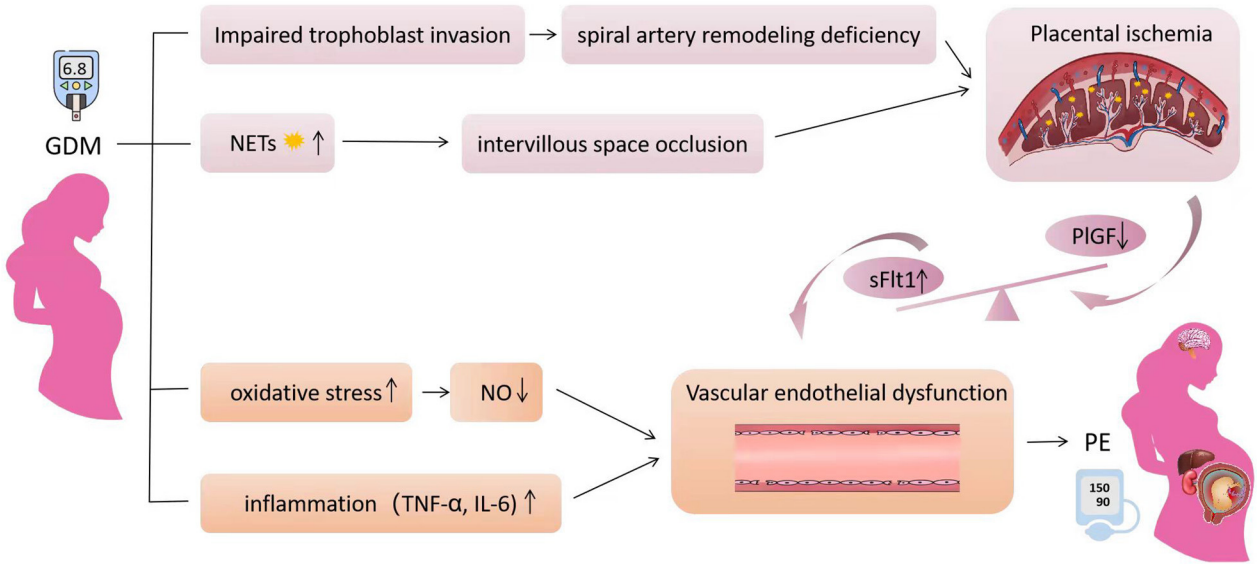

FIGURE 1 | The mechanism of gestational diabetes mellitus affecting the occurrence of preeclampsia. Hyperglycemia inhibits trophoblast migration and invasion by inducing trophoblast inflammation and autophagy, which can lead to uterine spiral artery remodeling deficiency. Neutrophils in GDM are over-activated and release excessive neutrophil extracellular traps resulting intervillous space occlusion. The two factors cause placental ischemia and hypoxia, resulting in the imbalance of anti-angiogenic factors, which can lead to vascular endothelial injury. In addition, increased oxidative stress in GDM leads to decreased nitric oxide synthesis and activity, resulting in vasodilation dysfunction. The increased inflammatory factors further aggravate the vascular endothelial injury. The clinical symptoms of preeclampsia eventually appeared, including hypertension and multiple organ injury. Obesity exaggerates all pathways affecting PE.

GDM complicated with PE (186). However, whether it can early identify the risk of PE in women with GDM needs further research. In conclusion, there are no practical markers to predict the occurrence of PE in women with GDM, and we need to explore the pathophysiology of GDM and PE further.

CONCLUSION

In most studies, GDM is independently associated with PE in singleton pregnancy, and pre pregnancy BMI and blood glucose levels are closely related with the occurrence of PE. Therefore, optimizing the treatment and management of GDM can reduce the incidence of PE. Oral hypoglycemic drugs, including metformin and glibenclamide, showed no significant difference in the occurrence of PE compared with insulin, despite a decreasing trend for metformin. The effects of GWG on PE, especially after the diagnosis of GDM and early-onset GDM, are controversial, and thus warrant further prospective studies. Twin pregnancy and PCOS significantly increased the occurrence of PE in women with GDM. However, GDM has less effect on PE in twin pregnancy and pregnant women with PCOS. The prevalence of GDM is significantly increased, which also increases the incidence of PE. Therefore, identifying the controllable factors affecting PE of GDM is important for improving pregnancy outcomes. GDM may affecting the occurrence of PE by inducing placental ischemia, increasing oxidative stress and inflammation. Understanding the pathophysiological mechanism of GDM affecting the occurrence of PE is helpful to find effective markers and preventive measures, which needs further studies.

AUTHOR CONTRIBUTIONS

YY collected material and wrote the first draft. NW contributed to design of the study and provided critical feedback. All authors contributed to the article and agree to be accountable for the content of the work.

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Value of the Systemic Immune-Inflammatory Index (SII) in Predicting the Prognosis of Patients With Peripartum Cardiomyopathy

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Background: Peripartum cardiomyopathy (PPCM) is a potentially life-threatening complication of pregnancy. The identification of early prognostic markers in patients diagnosed with PPCM is very important. The systemic immune-inflammation index (SII) is a new inflammatory biomarker, and the aim of this study was to evaluate the prognostic value of SII in patients with PPCM.

Methods: A total of 61 patients with PPCM who were admitted in our hospital from 2015 to 2020 were retrospectively analyzed in this study. The follow-up period of all patients was at least 6 months after diagnosis. Recovery of left ventricular (LV) systolic function was defined as the presence of left ventricular ejection fraction $> 45\%$. The second endpoint was defined as composite adverse cardiac events, including cardiac death or hospitalization due to worsening heart failure. Univariate and multivariate logistic regression analysis were used to determine the independent predictors of non-recovery of LV systolic function. The receiver operating characteristic (ROC) curve analysis was used to establish a cut-off level of SII value to predict persistent LV systolic dysfunction.

Results: The follow-up duration was 40.5 ± 16.3 months. Among the 61 patients, 43 patients showed left ventricular recovery and 18 patients did not at the last follow-up visit. The baseline SII levels were significantly higher in the non-recovery group ($P < 0.05$). Multivariate logistic regression showed that the SII and left ventricular end-diastolic dimension (LVEDD) were independent predictors of persistent LV systolic dysfunction (OR: 1.177, 95% CI: 1.038–1.335, $P = 0.011$ and OR: 1.148, 95% CI: 1.011–1.304, $P = 0.033$, respectively). A SII value of 876 was the best cut-off value (the area under the curve was 0.791, 95% CI: 0.667–0.915, $P < 0.05$), and the sensitivity and specificity were 73 and 71%, respectively.

Conclusions: The SII and LVEDD are independent prognostic factors for persistent LV systolic dysfunction in patients with PPCM. The SII may be a useful tool for identifying high-risk PPCM patients.

Keywords: peripartum, cardiomyopathy, heart failure, prognosis, systemic immune inflammatory index

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INTRODUCTION

Peripartum cardiomyopathy (PPCM) is a potentially pathogenic disease, usually characterized by heart failure (HF) with decreased ejection fraction in the last month of pregnancy or a few months after delivery (1). Global estimates of the incidence of PPCM vary by region, with reports ranging from 1 in 102 deliveries in Nigeria, to 1 in 10,000 deliveries in Denmark. In the US, its incidence has been estimated at 10.3 per 10,000 live births, and the trend is increasing over time (2). The etiology of PPCM is not clearly known, and it may include possible factors such as inflammation, autoimmune response, imbalance of oxidative stress, induction of antiangiogenic factors, viral infections, and cytokines activation (1, 3).

PPCM can cause serious consequences, including cardiogenic shock, thromboembolism, mechanical circulatory support, cardiac transplantation, and death (1). Although clinical manifestations and outcomes of PPCM vary widely, clinical investigations showed that left ventricular (LV) recovery occurred in 23–66% depending on the study size, race, and follow-up duration. In some studies, almost all recovery of left ventricular function occurred within 6 months after diagnosis, and other studies have also reported delayed recovery of left ventricular function (4). There are many studies to explore the predictors of left ventricular recovery in patients with PPCM. A number of studies have reported that increased left ventricular end-diastolic diameter (LVEDD), decreased baseline left ventricular ejection fraction (LVEF), older age, late diagnosis, black race and elevated inflammatory plasma markers predicted poor prognosis and lower recovery possibility in patients with PPCM (5, 6). However, predicting which patients will have complete left ventricular recovery and which will develop persistent left ventricular systolic dysfunction is still difficult. Therefore, the identification of early prognostic indicators in patients diagnosed with PPCM is very important in risk stratification, prevention of complications and improvement of prognosis.

The systemic immune-inflammation index (SII) is a new biomarker of inflammation, which is calculated as (neutrophil count) × (platelet count)/(lymphocyte count). SII integrates peripheral lymphocyte, neutrophil and platelet counts into one index, to better reflect the balance between inflammation and immunity (7). SII has been proven to be a powerful prognostic indicator of many types of cancer, and it is a useful prognostic index (8). In several studies, SII was found to be a prognostic marker of coronary heart disease (9, 10). However, the prognostic value of SII in PPCM patients has not been proposed before. The purpose of this study was to evaluate the prognostic value of SII in patients with PPCM for the first time.

MATERIALS AND METHODS

Study Population

A total of 61 patients who were diagnosed with PPCM in our tertiary reference center between January 2015 and December 2020 were included in this retrospective analysis. Demographic parameters, laboratory and echocardiogram data of all the patients were reviewed from their patient files, clinical follow-up visits and electronic database. The study protocol was reviewed and approved by the institutional ethics committee in accordance with the Declaration of Helsinki. PPCM was defined as an occurrence of unexplained HF with LVEF $< 45\%$, presenting toward the end of pregnancy or in the months after delivery, abortion or miscarriage in previously healthy women (11). All women were at least 18 years of age. The study exclusion criteria were as follows: (1) patients with valvular heart disease, (2) patients with congenital heart disease, (3) patients with ischemic cardiomyopathy, (4) history of malignant tumors and rheumatic diseases. The follow-up duration was at least 6 months after diagnosis of PPCM. A patient will be considered to have high blood pressure if her blood pressure is ≥140/90 mmHg or taking any anti-hypertensive drug.

All patients underwent two-dimensional and M-mode echocardiography, as well as continuous, pulsed and color Doppler echocardiography at the time of diagnosis and the last follow-up visit. Echocardiographic parameters such as LVEF, LVEDD, and left atrium diameter (LAD) were recorded for statistical analysis.

Blood samples were collected at baseline and laboratory tests were performed. The tests included neutrophil, lymphocyte and platelet counts, N-terminal B-type natriuretic peptide (NT-proBNP), erythrocyte sedimentation rate (ESR), low-density lipoprotein cholesterol (LDL-C), etc. SII was calculated as (neutrophil count) × (platelet count)/(lymphocyte count).

Recovery of LV systolic function was defined as the presence of LVEF $> 45\%$, while non-recovery (persistent LV systolic dysfunction) was defined as the presence of LVEF $\leq 45\%$ at last follow-up visit. The second endpoint was defined as composite adverse cardiac events, including cardiac death or hospitalization due to worsening HF.

Statistical Analysis

Data were analyzed using the SPSS 26.0 Statistical Package Program for Windows (SPSS, Inc., IL, USA). Continuous variables were presented as mean ± standard deviation (SD) or median with interquartile ranges. Categorical variables were presented as frequency and percentage. Kolmogorov–Smirnov test was used to test normality of distribution. Student's *t*-test was used to compare continuous variables between groups for normally distributed variables and Mann–Whitney *U*-test for variables without normal distribution. The Chi-square or Fisher's Exact test was used to compare categorical variables as appropriate. Univariate and multivariate logistic regression analysis was used to assess the capability of the individual variables to predict persistent LV systolic dysfunction. The receiver operating characteristic (ROC) curve analysis was used to establish an optimum cut-off level of admission SII values to predict persistent LV systolic dysfunction. A *p*-value 0.05 was considered statistically significant.

RESULTS

A total of 61 patients diagnosed with PPCM were enrolled in our study. The mean follow-up period was 40.5 ± 16.3 months.

The mean age of diagnosis was 31.8 ± 5.2 years. The proportion of New York Heart Association (NYHA) functional class 2–4 was 7 cases (11.5%), 17 cases (27.9%), and 37 cases (60.6%). Six patients (9.8%) had cardiogenic shock during initial diagnosis. Most of the patients had an onset of PPCM before delivery (36, 59%), and 25 patients (41.0%) presented in the postpartum period, in which 9 cases occurred after spontaneous delivery and 16 cases were after a cesarean section. In terms of the parity, 22 patients (36.1%) were primiparous while 35 patients have had 2 births (57.4%), 3 patients 3 births (4.9%), and 1 patient 4 births (1.6%). Three cases (4.9%) involved twin pregnancies. Among the patients, 30 cases (49.2%) were complicated with gestational hypertension and 6 cases (9.8%) were complicated with diabetes. Most patients received routine treatment of HF, including diuretics, β-blockers, and angiotensin converting enzyme inhibitor/angiotensin receptor blocker (ACEI/ARB). No significant differences were observed between the two groups when using either diuretics, β-blockers or ACEI/ARB. In our study, none of the patients with PPCM were treated with bromocriptine and mechanical circulatory support.

At the last follow-up visit, 43 patients showed LV function recovery and 18 patients did not at the last follow-up visit. In non-recovery group, 7 patients were re-hospitalized due to worsening HF, 1 patient was dead after ventricular fibrillation. In recovery group, 17 patients (39.5%) were recovered in the first 6 months and 26 patients (60.5%) had LV function recovery more than 6 months. The mean recovery duration was 21.0 ± 16.7 months. After 12–24 months of recovery of LV function, 4 patients stopped the therapy and 18 patients gradually reduced the dose of spironolactone, ACEI/ARB and β-blockers. After 6–24 months of follow-up, there was no significant effect on the LV function after change in therapy in these patients. There were no significant differences in age, cardiogenic shock during initial diagnosis or complications of hypertension between the two groups. The SII

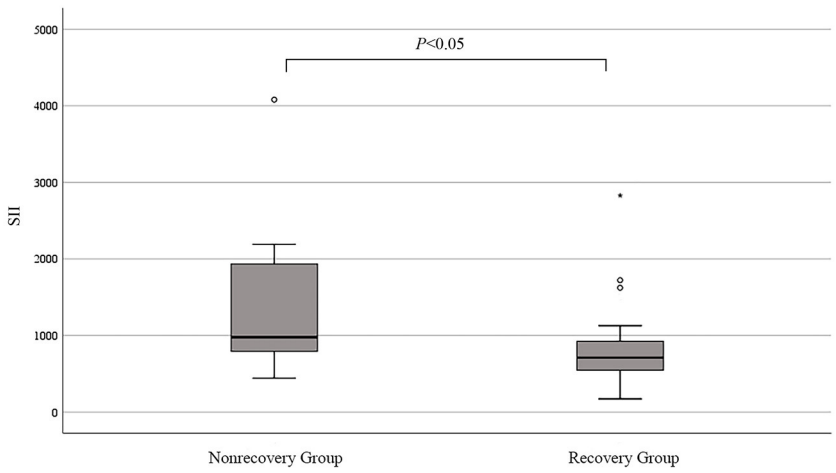

FIGURE 1 | Median SII in non-recovery and recovery groups. °mild outliers; *extreme outliers.

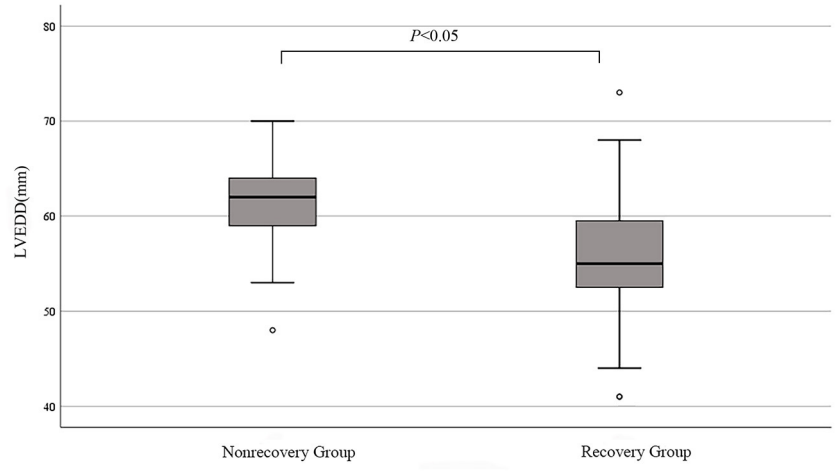

FIGURE 2 | Median LVEDD in non-recovery and recovery groups. °mild outliers.

TABLE 1 | Baseline clinical, echocardiogram, and laboratory data of patients with and without LV recovery.

	Recovery group ($n = 43$)	Non-recovery group ($n = 18$)	*P*-value
Age (year)	32.1 ± 5.0	31.0 ± 5.6	0.436
Presented at postpartum period, *n* (%)	17 (39.5%)	8 (44.4%)	0.722
Hypertension, *n* (%)	24 (55.8%)	6 (33.3%)	0.109
Cardiogenic shock, *n* (%)	2 (4.7%)	4 (22.2%)	0.057
β-blockers, *n* (%)	36 (83.7%)	15 (83.3%)	0.970
ACEI/ARB, *n* (%)	35 (81.4%)	11 (61.1%)	0.176
Spironolactone, *n* (%)	28 (65.1%)	10 (55.6%)	0.680
Systolic blood pressure (mmHg)	132 ± 23	126 ± 25	0.377
BMI (kg/m^2)	28.09 ± 4.92	30.06 ± 4.99	0.298
NT-proBNP (pg/mL)	3,134 (667–5,510)	5,365 (870–8836)	0.174
Neutrophil (×10^9/L)	5.66 (3.70–7.46)	7.33 (5.96–8.36)	0.075
Lymphocyte (×10^9/L)	1.98 ± 0.75	2.07 ± 1.03	0.890
Platelets (×10^9/L)	256 (188–339)	304 (269–383)	0.071
Monocyte (×10^9/L)	0.47 (0.33–0.60)	0.51 (0.35–0.70)	0.319
Hemoglobin (g/L)	119 (111–133)	117 (104–124)	0.169
ESR (mm/h)	34.1 ± 19.2	52.7 ± 33.3	0.200
Procalcitonin (ng/mL)	0.19 (0.05–0.40)	0.25 (0.13–0.54)	0.696
D-Dimer (μg/mL)	1.13 (0.62–2.74)	1.01 (0.77–2.22)	0.725
ALT (U/L)	25 (17–38)	25 (14–50)	0.800
Albumin (g/L)	33.2 ± 6.2	35.5 ± 4.0	0.095
Uric acid (μmol/L)	447.1 ± 164.1	335.9 ± 137.6	0.048
Creatinine (μmol/L)	61 (50–75)	60 (52–70)	0.675
Potassium (mmol/L)	4.09 (3.80–4.41)	4.10 (3.74–4.45)	0.843
LDL-C (mmol/L)	3.1 ± 1.1	2.8 ± 0.8	0.448
Homocysteine (μmol/L)	13.2 (10.53–17.00)	13.9 (12.2–17.1)	0.650
LDH (U/L)	342 (268–505)	345 (254–426)	0.712
FT3 (pmol/L)	3.6 (3.0–4.2)	3.3 (2.9–3.9)	0.357
FT4 (pmol/L)	12.4 (10.8–14.9)	13.7 (11.2–14.8)	0.673
CK-MB (ng/mL)	1.7 (0.9–4.1)	1.0 (0.9–1.3)	0.220
LVEF (%)	33 ± 10	28 ± 11	0.065
LAD (mm)	40.7 ± 6.0	41.2 ± 5.6	0.832
LVEDD (mm)	55.7 ± 6.9	61.0 ± 6.6	0.022
SII	710 (545–953)	978 (785–1,953)	0.023
SII>876, *n* (%)	13 (30.2%)	12 (66%)	0.008

ACEI/ARB, angiotensin converting enzyme inhibitors/angiotensin receptor blocker; BMI, body-mass index; NT-proBNP, N-terminal B-type natriuretic peptide; ESR, erythrocyte sedimentation rate; ALT, Alanine aminotransferase; LDL-C, low-density lipoprotein cholesterol; LDH, lactate dehydrogenase; FT3, free thyroid threeiodine; FT4, free thyroxine; CK-MB, Creatine Kinase Isoenzyme-MB; LVEF, left ventricular ejection fraction; LAD, left atrium diameter; LVEDD, left ventricular end-diastolic dimension; SII, systemic immune-inflammation index.

of the non-recovery group was significantly higher than that of the recovery group (**Figure 1**). In addition, LVEDD increased in the non-recovery group (**Figure 2**). As components of SII calculation, there were no statistical differences in the neutrophil, lymphocyte and platelet counts. Uric acid level in non-recovery group was significantly lower compared to the group with recovery of LV function ($P = 0.048$). Other laboratory parameters and echocardiographic parameters were similar between the two groups (**Table 1**).

Table 2 presents primary and secondary clinical endpoints according to SII values. During follow-up period, patients in the high SII group had a higher incidence of persistent LV systolic dysfunction (48 vs. 16.7%; $P = 0.008$). Secondary endpoint was significantly higher in the group with high SII (24 vs. 5.6%; $P = 0.044$). Cardiac death only happened in the group with high SII (4 vs. 0%). Re-hospitalization due to worsening HF developed more frequently in the high SII group (20 vs. 5.6%).

The univariate and multivariate logistic regression analysis for the two groups are presented in **Table 3**. The variables that were significant in the univariate logistic regression analysis ($P < 0.05$) were included in the multivariate analysis. Only SII and LVEDD were identified as independent predictors of persistent LV systolic dysfunction in patients with PPCM (OR: 1.177, 95% CI: 1.038–1.335, $P = 0.011$ and OR: 1.148, 95% CI: 1.011–1.304, $P = 0.033$, respectively).

According to the ROC curve analysis, the best cut-off value was 876. After this level, PPCM patients had a higher rate of persistent LV systolic dysfunction (sensitivity 73%, specificity

TABLE 2 | Primary and secondary clinical endpoints according to SII.

	High SII (>876) (*n* = 25)	Low SII (<876) (*n* = 36)	*P*-value
Persistent LV systolic dysfunction, *n* (%)	12 (48%)	6 (16.7%)	0.008
Second endpoint, *n* (%)	6 (24%)	2 (5.6%)	0.044
Cardiac death, *n* (%)	1 (4%)	0 (0%)	0.410
Re-hospitalized due to worsening HF, *n* (%)	5 (20%)	2 (5.6%)	0.112

TABLE 3 | Univariate and multivariate logistic regression analysis for non-recovery and recovery groups.

	OR	95%CI	*P*-value
Univariate logistic regression			
Age	0.957	0.859–1.064	0.430
Onset in the postpartum period	1.350	0.442–4.123	0.598
Hypertension	2.200	0.691–7.006	0.182
Parity	0.661	0.262–1.666	0.380
β-blockers	0.972	0.221–4.273	0.970
ACEI/ARB	0.359	0.106–1.216	0.100
Spironolactone	0.670	0.218–2.055	0.483
Systolic blood pressure	0.989	0.966–1.013	0.372
BMI	1.087	0.930–1.271	0.294
Neutrophil	1.178	0.974–1.425	0.092
Lymphocyte	1.049	0.539–2.042	0.888
Platelets	1.004	0.999–1.010	0.132
Hemoglobin	0.973	0.942–1.005	0.093
ESR	1.034	0.994–1.075	0.095
Procalcitonin	0.861	0.494–1.502	0.598
D-Dimer	0.797	0.556–1.141	0.215
Albumin	1.077	0.971–1.195	0.161
LDL-C	0.777	0.410–1.474	0.440
CK-MB	0.930	0.733–1.181	0.548
LVEF	0.948	0.894–1.004	0.070
LAD	1.012	0.907–1.130	0.827
LVEDD	1.127	1.011–1.257	0.031
SII	1.093	1.008–1.184	0.031
Multivariate logistic regression			
SII	1.177	1.038–1.335	0.011
LVEDD	1.148	1.011–1.304	0.033

ACEI/ARB, angiotensin converting enzyme inhibitors/angiotensin receptor blocker; BMI, body-mass index; ESR, erythrocyte sedimentation rate; LDL-C, low-density lipoprotein cholesterol; CK-MB, Creatine Kinase Isoenzyme-MB; LVEF, left ventricular ejection fraction; LAD, left atrium diameter; LVEDD, left ventricular end-diastolic dimension; SII, systemic immune-inflammation index.

71%), as shown in **Figure 3**. The area under the ROC curve was 0.791 (95% CI: 0.667–0.915, $P < 0.05$).

Table 4 presents baseline clinical, echocardiogram, and laboratory data of recovery group who had recovery within or more than 6 months. There were no significant differences in SII between two groups ($P = 0.187$), but SII in the delayed group has a higher tendency than the other group. Patients with higher NT-proBNP, higher homocysteine (Hcy), and higher lactate dehydrogenase (LDH) were more likely to have delayed recovery of LV function (NT-proBNP: $P = 0.039$, Hcy: $P = 0.027$, LDH: $P = 0.008$).

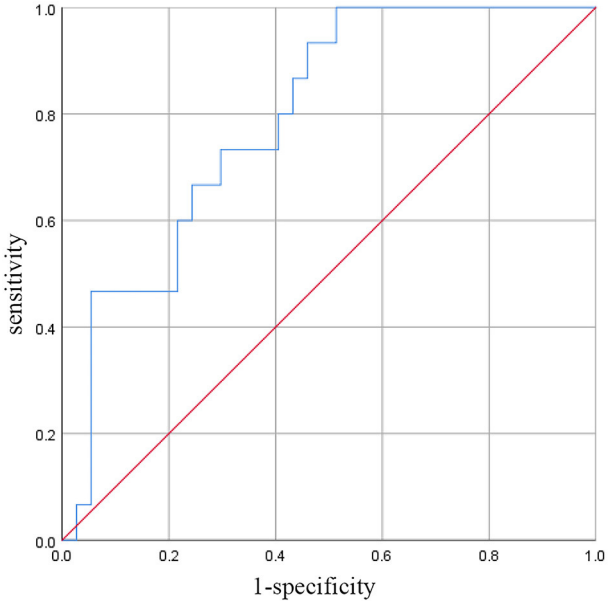

FIGURE 3 | ROC curve of the SII for predicting persistent LV systolic dysfunction.

DISCUSSION

In the present study, we found that the SII of the non-recovery group was significantly higher than that of the recovery group, which was an important predictor of LV recovery. ROC analysis showed that the cut-off value of SII for predicting persistent LV systolic dysfunction was 876. As far as we know, this study is the first to determine the long-term prognostic value of SII in patients with PPCM.

PPCM is a potentially life-threatening disease, usually characterized by HF with decreased ejection fraction in the last month of pregnancy or a few months after delivery. In 2010, the Study Group on peripartum cardiomyopathy of the Heart Failure Association (HFA) of the European Society of Cardiology (ESC) defined PPCM as an idiopathic cardiomyopathy occurring toward the end of pregnancy or in the months following delivery, abortion or miscarriage, without other causes for HF, and with a LVEF <45% (11). The incidence in China is one in 346 live births, but that calculation is only based on data from a tertiary reference center, so this subject needs to be studied on a larger scale (12).

Risk factors for PPCM include multiparity and multiple pregnancies, family history, race, smoking, diabetes, hypertension, pre-eclampsia, malnutrition, and age of the mother (4). The etiology of PPCM is uncertain. The possible factors may include inflammation, autoimmune response, imbalance of oxidative stress, induction of antiangiogenic factors, viral infections, and cytokines activation (1, 3). One

TABLE 4 | Baseline clinical, echocardiogram, and laboratory data of recovery group who had recovery within or more than 6 months.

	<6 months ($n = 17$)	>6 months ($n = 26$)	*P*-value
Age (year)	31.2 ± 4.3	32.8 ± 5.4	0.313
Presented at postpartum period, *n* (%)	5 (29.4%)	12 (46.2%)	0.272
Hypertension, *n* (%)	13 (76.5%)	11 (42.3%)	0.059
Systolic blood pressure (mmHg)	137 ± 26	128 ± 22	0.265
BMI (kg/m^2)	27.38 ± 5.41	29.01 ± 4.23	0.362
NT-proBNP (pg/mL)	1,534 (315–3,487)	4,108 (1,785–6,809)	0.039
Neutrophil (×10^9/L)	5.55 ± 2.24	6.24 ± 2.84	0.404
Lymphocyte (×10^9/L)	1.90 (1.50–2.58)	1.80 (1.44–2.56)	0.794
Platelets (×10^9/L)	203 (158–333)	275 (235–339)	0.062
Monocyte (×10^9/L)	0.47 (0.33–0.62)	0.47 (0.32–0.59)	0.852
Hemoglobin (g/L)	118 ± 11	121 ± 20	0.633
ESR (mm/h)	46.4 ± 23.1	29.9 ± 16.6	0.098
Procalcitonin (ng/mL)	0.23 (0.08–0.33)	0.10 (0.04–0.89)	0.804
D-Dimer (μg/mL)	1.08 (0.40–2.02)	1.17 (0.75–3.32)	0.376
ALT (U/L)	26 (19–40)	24 (14–37)	0.576
Albumin (g/L)	33.6 ± 6.7	32.9 ± 6.1	0.738
Uric acid (μmol/L)	348.9 ± 99.1	492.9 ± 170.7	0.053
Creatinine (μmol/L)	59 (50–68)	68 (50–87)	0.117
Potassium (mmol/L)	4.11 (3.80–4.64)	4.08 (3.80–4.40)	0.371
LDL-C (mmol/L)	3.1 ± 0.9	3.0 ± 1.2	0.842
Homocysteine (μmol/L)	11.8 (8.3–12.8)	15.4 (11.2–20.2)	0.027
LDH (U/L)	264 (239–309)	388 (294–530)	0.008
FT3 (pmol/L)	3.4 (3.0–4.1)	3.7 (2.9–4.2)	0.967
FT4 (pmol/L)	11.9 (10.9–13.0)	13.1 (10.6–15.8)	0.267
CK-MB (ng/mL)	1.7 (1.1–3.1)	1.5 (0.6–4.4)	0.960
LVEF (%)	36 ± 7	30 ± 10	0.056
LAD (mm)	40 (32–46)	41 (39–44)	0.482
LVEDD (mm)	54.3 ± 4.4	56.9 ± 8.3	0.280
SII	674 (514–807)	801 (565–1,045)	0.187

BMI, body-mass index; NT-proBNP, N-terminal B-type natriuretic peptide; ESR, erythrocyte sedimentation rate; ALT, Alanine aminotransferase; LDL-C, low-density lipoprotein cholesterol; LDH, lactate dehydrogenase; FT3, free thyroid threeiodine; FT4, free thyroxine; CK-MB, Creatine Kinase Isoenzyme-MB; LVEF, left ventricular ejection fraction; LAD, left atrium diameter; LVEDD, left ventricular end-diastolic dimension; SII, systemic immune-inflammation index.

theory suggests that the oxidative stress-mediated cleavage of the hormone prolactin into 16-kDa prolactin, which is a smaller antiangiogenic subfragment, may drive PPCM by inducing endothelial damage. 16-kDa prolactin can also induce to release endothelial microparticles containing active compounds, such as microRNAs, into the circulation and may subsequently impair cardiomyocyte metabolism and further promote the occurrence of PPCM (13, 14). Studies have shown that partial or complete recovery of left ventricular function occurred in many patients with PPCM. However, PPCM can also cause serious consequences, including cardiogenic shock, thromboembolism, mechanical circulatory support, heart transplants and death (1). There is still no specific and accurate predictor of PPCM cardiac recovery. Some factors that predict the prognosis of patients with PPCM have been proposed before, such as increased NT-proBNP, prolonged QT intervals and sinus tachycardia in electrocardiography (ECG), decreased LVEF, enlarged LV, decreased systolic blood pressure and increased resting heart rate at the time of diagnosis, however this suggestions have not been verified (15–17).

Studies have demonstrated evidence of inflammatory processes and immune responses characterized by cytokine imbalance associated with PPCM (18). Inflammation can be measured with a variety of hematological and biochemical markers. Some studies have shown that increased plasma markers of inflammation and apoptosis at diagnosis were predictors of poor prognosis of PPCM. Some studies found that baseline C-reactive protein (CRP), tumor necrosis factor-α (TNF-α), and interleukin-6 (IL-6) were associated with mortality in patients with PPCM (19, 20). Lymphocyte, neutrophil, and platelet counts are markers that vary with the severity of inflammation and oxidative stress. In recent years, a new index, SII, was proposed based on circulating immune inflammatory cells such as platelets, neutrophils and lymphocytes, which can reflect the balance between the host's inflammatory and immune status better. The SII were thought to be more specific than CRP or the ESR. It is widely reported that SII has been proven to be a powerful prognostic indicator of many kinds of cancer (8). SII has been found to be a prognostic marker of cardiovascular diseases. A number of studies have shown that SII is associated with poor clinical outcomes of various cardiovascular diseases, including acute coronary syndrome, ST segment elevation and non-ST segment elevation myocardial infarction. Studies have shown that a higher SII is independently associated with future risk of cardiac death, non-fatal myocardial infarction, non-fatal stroke or hospitalization due to HF in patients with coronary artery disease (CAD), and it has a better predictive effect on major cardiovascular events after percutaneous coronary intervention (9, 10). SII can also predict the severity of coronary artery stenosis (21). However, the role of SII as a newly available inflammation-based marker in predicting LV recovery in PPCM has not been evaluated. In our study, the SII of the non-recovery group was significantly higher than that of the recovery group. High SII and increased LVEDD were found to be important predictors of predicting persistent LV systolic dysfunction. Our results suggest that this index can be used to determine the risk of adverse outcomes in patients with PPCM and guide the selection of treatment. Uric acid level in non-recovery group was significantly lower compared to the group with recovery of LV function. We think that this is a chance event due to the small sample size of patients and larger research is needed. The SII cannot predict early or delayed recovery of LV function in the present study, and we think this subject needs to be studied on a larger scale. NT-proBNP, Hcy, and LDH were increased in delayed recovery group. NT-proBNP can predict the prognosis of patients with PPCM have been proposed before (15), but the relationship between Hcy, LDH and PPCM have not been reported before. This phenomenon needs to be further researched. From a clinical point of view, as a new predictor of inflammation and oxidative stress,

special attention should be given to SII in the initial evaluation of PPCM.

After LV function recovery of PPCM patients, how long the medical therapy should continue is still unknown. In 2019, the Study Group on PPCM of the HFA of the ESC proposed that a combined therapy regimen should be maintained until 12–24 months after full recovery of LV function (11). In our study, the PPCM patients who stopped or gradually reduced the medical therapy 12–24 months of recovery of LV function has not experienced worsening of LV function so far. However, long-term follow-up is necessary to determine further effects on cardiac function.

Our research has some limitations. The main limitation of this study is that our data came from single-center registrations, and the number of patients was relatively small due to the rarity of PPCM. Hence, the statistical power of some observations may be limited. In addition, prolactin and other inflammatory markers, such as IL-6 and TNF-α, were not measured because they are not usually available in daily practice. Another limitation of this study was that SII levels were evaluated only once and changes in SII were not assessed over time during follow-up visits.

CONCLUSIONS

Increased SII and increased LVEDD are independent prognostic factors for persistent LV dysfunction in patients with PPCM. SII may help to identify high-risk patients with PPCM. The advantages of SII include low cost, simple calculation and good repeatability, so it can be widely used to predict the recovery of LV function. However, our findings should be confirmed in prospective, larger research involving other inflammatory biomarkers to clearly explain the exact role of SII in PPCM.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

AUTHOR CONTRIBUTIONS

YZ: conception and design and data analysis and interpretation. YT and PB: administrative support. YZ, WL, HY, ZC, and CZ: provision of study materials or patients and collection and assembly of data. All authors writing the manuscript and final approval of manuscript.

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Periodontal Inflamed Surface Area Is Associated With Increased Gestational Blood Pressure and Uric Acid Levels Among Pregnant Women From Rural North China

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Background: Periodontal disease has been associated with gestational complications and both conditions have a high prevalence in rural populations from developing regions. A cross-sectional study was carried out to explore the relationship between periodontal inflamed surface area (PISA), blood pressure (BP), and, serum uric acid levels (UA) in a group of rural North Chinese pregnant women in the third trimester of pregnancy.

Methods: Three hundred and thirty-five rural women aged 20–34 years, with normal body mass index (BMI) were examined in a cross-sectional study during their third trimester of gestation. Exclusion criteria were history of pregnancy complications, multiple pregnancy, smoking habits, diabetes, hypertension or any known infectious disease. Socio-demographic variables, including age and socioeconomic status (SES), systolic blood pressure (SBP) and diastolic blood pressure (DBP) readings, serum UA levels, and PISA values were recorded. A structural equation model was implemented with two constructed latent variables including "Dem" (comprising of age and SES category to represent unobserved demographic variables) and, "BP" (comprising of SBP and DBP to account for measurement error and lack of multiple BP readings). The model accounted for co-variance of BP and UA, and implemented simultaneous regressions for BP and UA as outcomes, upon Dem and PISA values as exogenous variables.

Results: The median PISA score was 1,081.7 (IQR = 835.01), reflecting high levels of periodontal inflammation in the sample. SEM showed a significant association of PISA with BP (estimate = 0.011, 95% CI = 0.009–0.012 $p < 0.001$) and UA (estimate = 0.001, 95% CI = 0.001–0.001, $p < 0.001$).

Conclusion: Higher PISA values were significantly associated with higher blood pressure and uric acid levels among rural pregnant women in a cross-sectional sample from a center in North China after accounting for a latent demographic construct derived from age and SES.

Keywords: periodontal disease, low birth weight, gestational hypertension, uric acid, periodontal inflamed surface area

INTRODUCTION

Hypertensive disorders of pregnancy affect more than 5% of women in China, with the highest incidence in North China (1). Hypertension without the development of significant proteinuria (<0.3 g/l), after 20 weeks of gestation or during labor and/or within 48 h of delivery is termed gestational hypertension and is a risk for preeclampsia, eclampsia, and preterm low birth weight (2). Inflammation has been implicated in the pathogenesis of preeclampsia and attributed to chronic subclinical infections and higher levels of pro-inflammatory cytokines (3). Principally, gestational blood pressure and increased oxidative stress are interlinked (4) and both are associated with a higher risk of adverse pregnancy outcomes (5). Chronic infections are established contributors to these, operating through increased systemic pro-inflammatory cytokine load (6). Serum uric acid, a primary physiological antioxidant is considered as one of the primary markers of oxidative stress (7) and hyperuricemia in pregnancy is implicated both as a risk marker and contributory factor for preeclampsia (8). In particular, increased blood pressure during the third trimester of pregnancy is linked to adverse birth outcomes (9).

Periodontal infection is a source of chronic systemic microbial load and has been associated with the incidence of preeclampsia (10) and pre-term low birth weight infants (11). Proposed mechanisms of the periodontal infection-pregnancy outcome link include oral bacterial translocation to the uteroplacental unit, increased systemic oxidative stress and pro-inflammatory cytokine load leading to preeclampsia and premature rupture of membranes (12). A major contributory mechanism is the systematic dissemination and placental localization of periodontal pathogens such as *Porphyromonas gingivalis* with ensuing immuno-inflammatory sequelae (9, 13). Umbrella reviews of systematic reviews have noted that periodontal disease increases the odds of pre-eclampsia (14) and pre-term birth (15) by ∼2-fold but also show that several meta-analyses have not adjusted for confounding. Heterogeneity in the strength association depends on the nature of exposure and outcome variables analyzed (16, 17). At the same time, current evidence evaluating the efficacy of periodontal treatment in reducing adverse pregnancy outcomes is unclear and incongruent (18–22). An umbrella review found significant effects upon subgroup analysis based on sociodemographic conditions (23), which highlights the significance of studying vulnerable populations in this context.

Periodontal disease can be highly prevalent among pre-conception women in some regions of China (24), compounded by low levels of oral health awareness and utilization of dental services in rural areas (25). Periodontal disease has been reported to have a high prevalence among rural pregnant women in China (26). Therefore, its potential impact on pregnancy-related variables and outcomes in rural Chinese populations needs greater investigation. In addition, a large-scale retrospective study showed an increased risk of hypertension was associated with periodontal disease in the Chinese population (27), further highlighting the necessity of investigating periodontal disease as an exposure in the context of gestational blood pressure in Chinese populations. Higher prevalence of both periodontitis (24, 25) and hypertensive disorders during pregnancy (1) in populations in underserved regions of North China begets further investigations into their association.

Traditional measures of periodontal disease and disease categories pose limitations in assessing the burden of active inflammation which is responsible for its systemic sequelae, and therefore, the Periodontal Inflamed Surfaced Area (PISA) index was developed (28), representing the net probing depth of bleeding on probing positive sites for an individual. PISA values comprise a continuous quantitative variable that prevents the loss of information inherent to the categorization of periodontal disease categories (29). Moreover, different case-definition criteria applied for periodontal diagnosis in pregnant women yield widely variable disease estimates, and PISA may be a more suitable measure of inflammatory burden (30). Furthermore, periodontal inflammation as measured by PISA values has been associated with high blood pressure in a large-scale study of over 8,000 subjects (31).

The present cross-sectional study aimed to explore the association of periodontal inflammatory burden assessed using PISA values with prenatal gestational blood pressure and serum uric acid levels in a sample of rural-living North Chinese women in the third trimester of pregnancy.

MATERIALS AND METHODS

Ethical approval and sample size estimation: The study protocol was approved by the Medical Ethics Committee of Changzhi Medical College. All study procedures were compliant with the Declaration of Helsinki. Sample size estimation was performed using the "epi.sssimpleestb" function from the epidemilogical R packge "EpiR" (https://cran.r-project.org/web/packages/epiR/index.html). Data for the estimated prevalence of gestational hypertension in North China (7.44%) (1) was used to estimate the sample size, assuming a population of 1,000 suitable pregnant women would visit the sampling center during the data collection period. At a confidence interval of 95% and margin of error 20%, the target sample size was determined as 352. However, 335 subjects finally participated in the study as 17 recruited subjects were unable or unwilling to complete the study procedures.

Study Participants

A group of 335 eligible subjects in week 28 or beyond of pregnancy were recruited consecutively during their routine prenatal visit at The Heping Affiliated Hospital of Changzhi Medical College, Changzhi City, Shanxi Province, China, from January to April 2021. The inclusion criteria were; pregnant women aged between 18 and 34 years in the third trimester, Body Mass Index (BMI) of 18.5–24.9, presence of at least 20 teeth, with no history of periodontal or dental treatment in the past 1 year. Exclusion criteria were smoking or smoking habits, previous history of preterm delivery, previously diagnosed gestational hypertensive disorders, or other pregnancy complications, known systemic conditions or diseases such as

chronic hypertension, diabetes, renal disease, polyhydramnios or known congenital malformation in fetus, infections during pregnancy such as bacterial vaginosis and chorioamnionitis, other bacterial or viral illnesses, or antibiotic use during pregnancy. All subjects provided written and oral informed consent before any study procedure. Oral health counseling was provided to all screened subjects by a dental professional irrespective of their study participation. Appropriate referral for dental or medical management was also provided when deemed necessary based on the clinical findings.

Data Collection

Medical records were the source of demographic variables; age, socioeconomic level (SES), scored as high, medium or low, where to assess SES, monthly family income was noted and grouped into; low (<2,000 RMB per month), moderate (2,000–6,000 RMB per month) or High (6,000 RMB per month) (32), and retrospective medical data. The mean of three consecutive readings of blood pressure (SBP and DBP) was calculated and serum uric acid level (UA) was measured. A full mouth periodontal examination was performed by a trained single examiner (W.S) and included the recording of pocket probing depth (PPD), clinical attachment loss (CAL) and bleeding on probing (BOP) at 6 sites per tooth, by using a UNC-15 periodontal probe. PPD and CAL were measured as the linear distance in millimeters and rounded to the nearest millimeter, where PPD was the distance from the gingival margin to the base of the pocket and CAL was measured as the linear distance from the cementoenamel junction to the base of the pocket. Bleeding on probing (BOP) was recorded as a dichotomous variable representing presence of absence of bleeding. PISA values were calculated for each subject as described earlier (28) using an excel spreadsheet. In brief, the mean CAL and gingival recession for each tooth were recorded and were used to determine the periodontal epithelial surface area (PESA) score per tooth, representing the surface area in mm2 enveloped by pocket epithelium. Next, the PESA for score multiplied by the number of BOP positive sites around that tooth indicated the PISA score for that tooth, and the sum of these determined the full-mouth PISA score.

Data Analysis

All data analysis was performed in the R statistical environment. Prior to modeling, variable distribution was examined for normality using the Shapiro Wilk test. Structural equation modeling (SEM) was applied using the "lavaan" package (v 0.5-9) (33) using a maximum likelihood estimator. SEM is a multivariate modeling technique that allows simultaneous modeling of observed and unobserved or latent variables, and these variables can account for measurement error and observed covariation (34, 35). In the SEM model, UA, SBP, DBP were utilized as observed endogenous or dependent variables, and, age, SES and PISA were modeled as observed exogenous or independent variables. Two latent variables were created, including, "BP" as a combination of endogenous variables SBP and DBP, and "Dem" as a combination of exogenous variables age and SES. The co-variance of BP with UA was modeled to account for residual correlation. Two simultaneous regressions were modeled for BP and UA, using Dem and PISA values as predictors. Model fit was estimated as acceptable where Tucker-Lewis Index (TLI) > 0.90 (36) and normed Chi-square value <5 (37).

TABLE 1 | Descriptive statistics.

Parameter	Range	Median (interquartile range)
Age (years)	18–34	24 (6)
PISA value (mm^2)	0.0–2,472.6	1,081.7(835.01)
SBP (mm of Hg)	110–160	120 (5)
DBP (mm of Hg)	70–100	70 (10)
UA (mg/dl)	3.1–5.0	3.7 (0.6)
	Frequency	
SES	Low = 119 (35.5%), Medium = 216 (64.5%)	

PISA, Periodontal Inflamed Surface Area; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; UA, Serum Uric Acid; SES, Socioeconomic status.

RESULTS

Descriptive data pertaining to the cross-sectional sample are presented in **Table 1**. The median age of the cohort was 24 (IQR = 6) years. The distribution of SES showed that 119 (35.5%) were in low SES and 216 (64.5%) were in the medium SES category. The mean PISA score was 1,081.7 (IQR = 835.01). The median SBP was 120 (IQR = 5) and DBP was 70 (IQR = 10), while median UA was 3.7 mg/dl (IQR = 0.6). Based on SBP and DBP reading cut-offs for gestational hypertension (1, 2), 11.3% women satisfied the criteria and were referred for additional investigations. However, it was recognized that single day BP readings were not sufficient for definitive diagnosis; hence this grouping was not utilized for data analysis. Significant correlations between the observed variables are summarized in a correlation matrix plot presented in **Figure 1**. Significant and strong correlations ($r > 0.6$, $p < 0.001$, all) were noted between the three endogenous dependent variables DBP, SBP, and UA. Among the exogenous variables, age was significantly but weakly correlated with DBP ($r = 0.14$, $p = 0.01$), lower SES was weakly correlated with SBP ($r = 0.24$, $p < 0.001$), DBP ($r = 0.24$, $p < 0.001$) and UA ($r = 0.23$, $p < 0.001$). PISA score was moderately correlated with DBP ($r = 0.58$, $p < 0.001$) and strongly correlated with SBP ($r = 0.66$, $p < 0.001$) and UA ($r = 0.72$, $p < 0.001$). Very weak but significant correlations were noted for lower SES with Age ($r = 0.13$, $p = 0.02$) and PISA score ($r = 0.12$, $p = 0.03$). The SEM model outcomes are summarized in **Table 2**. The latent variable BP was highly significantly predicted by PISA (estimate = 0.011, 95% CI = 0.009–0.012, $p < 0.001$) and also significantly predicted by Dem (estimate = 3.37, 95% CI = 0.41–6.83, $p = 0.03$). UA was also significantly predicted by PISA (estimate = 0.001, 95% CI = 0.001–0.001, $p < 0.001$) and also significantly predicted by Dem (estimate = 0.15, 95%ci = 0.13–0.29, $p = 0.04$).

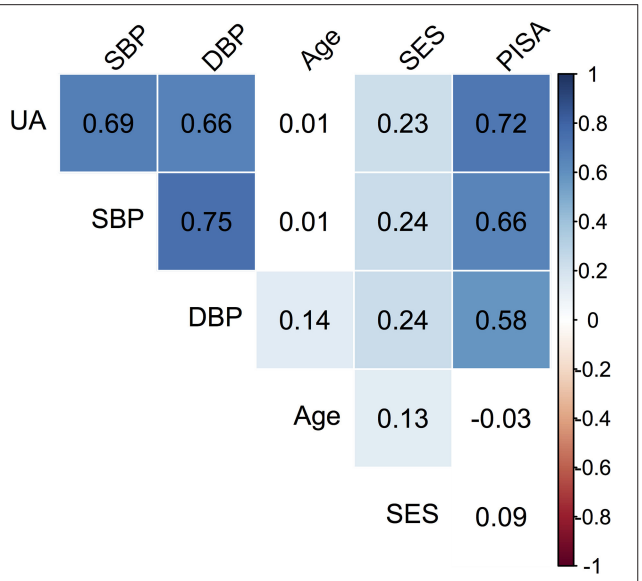

FIGURE 1 | Correlation matrix plot of the observed variables. The colored boxes represent significant *p*-values ($p < 0.05$), where the listed value corresponds to the correlation coefficient. White boxes represent non-significant correlations. For SES, the reference category is Medium (M).

TABLE 2 | Structural relationships and variances in the SEM[a] analysis.

Structural relationship	Estimate	95% CI	*P*-value
PISA ➜ BP[b]	0.011	0.009–0.012	<0.0001***
Dem[c] ➜ BP[b]	3.59	0.44–6.73	0.03*
PISA ➜ UA	0.001	0.001–0.001	<0.0001***
Dem[c] ➜ UA	0.15	0.13–0.28	0.04*
Variances			
SBP	18.45	12.78–24.13	<0.0001***
DBP	15.48	11.97–18.99	<0.0001***
UA	0.09	0.07–0.12	<0.0001***
Age	14.45	12.12–16.78	<0.0001***
SES*	0.14	0.05–0.24	0.003
BP	24.56	12.50–36.62	<0.0001***
Dem	0.70	−0.34–1.74	0.19

****p < 0.0001, *p < 0.05.*

[a] *Model fit indices: TLI = 0.96, normed Chi-square = 3.40.*

[b] *"BP" indicates a latent BP variable constructed from SBP and DBP.*

[c] *"Dem" indicates a latent Demographic variable constructed from Age and SES.*

PISA, Periodontal Inflamed Surface Area; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; UA, Serum Uric Acid; SES, Socioeconomic status.

DISCUSSION

This cross-sectional study explored the association of gestational blood pressure and UA, a marker of oxidative stress with periodontal inflammatory burden among pregnant women at a rural center in North China, using structural equation modeling. While the present study, identified the nature of the association between periodontal inflammation, BP and a marker of oxidative stress among rural women using a cross-sectional design, epidemiological studies have linked periodontal disease with a higher risk of pregnancy complications (10, 11, 14, 15, 17, 19) including preeclampsia and preterm low birth weight deliveries (38, 39). The type of periodontal disease case-definition may influence the outcome of an association of periodontal disease with pregnancy complications as noted by Papapanou and Ide (40), who also found that case-control and cross-sectional studies provided a higher estimate of the association as compared to prospective studies. Therefore, a strength of the current study is the utilization of PISA as an exposure variable indicating the inflammatory burden arising from periodontal disease. The median PISA score was 1,081.7 (IQR = 835.01), reflecting high levels of active periodontal inflammation in this sample, largely in agreement with previous findings of a very high prevalence of periodontal disease among rural Chinese pregnant women (41). Of note, A PISA value $\geq$ 130.33 mm^2 has been found to indicate periodontitis at very high sensitivity and specificity (42). Another strength of the present study is the use of SEM, a multivariate technique incorporating observed variables and latent constructs that allows for simultaneous modeling of multiple relationships and accounts for covariance between variables. Here, BP was modeled as a latent variable, as a trait derived from SBP and DBP (43), which can account for measurement errors inherent to the lack of longitudinal data, circadian pattern, and their correlation. Differences in circadian amplitudes of BP have been found to predict gestational complication even when BP readings were within physiological limits (44). In addition, 24-h BP during the third trimester has shown superior prediction of pregnancy complications than in-office BP readings, plausibly owing to the phenomenon of white coat hypertension (45). The restricted inclusion criteria were chosen to avoid the confounding effects of obesity, advanced age and other known systemic conditions. Age and income are established co-factors in the multi-factorial nature of gestational complications (46, 47) and were recorded. However, a number of confounding variables including the quality and regularity of prenatal care and diet that can influence gestational health. Considering these and other such variables were not assessed directly, a latent variable "dem" was constructed using maternal age and SES, as both of these factors are contributory to antenatal care utilization patterns, dietary variables, and pregnancy outcomes (48–50).

In the model, after accounting for the effects of latent demographic variables, higher gestational blood pressure was significantly associated with higher PISA values, in agreement with the results of Pietropaoli et al. (31) in the general population. Serum UA was also significantly associated with PISA score. Chronic infection and cytokine load have both been associated with increased xanthine oxidase activity (51) which is an important mediator of endogenous UA production. UA being a major plasma antioxidant and marker of systemic oxidative stress has been investigated with regards to periodontal disease and better periodontal status has been associated with higher levels of serum uric acid in healthy subjects (52). UA in pregnancy is considered an important risk marker of fetal risk in women with gestational hypertension (53)

and may have a causal role in its etiology (54). These findings suggest a contributory role of periodontal inflammatory burden to systemic oxidative stress and hypertension occurring during pregnancy.

The major limitations of the current study include the cross-sectional design that precludes causal inferences, the small sample size, and possible effects of unaddressed predictors such as nutritional status, lifestyle-related risk factors, genotype, the possibility of occult infection, level of antenatal care level, physical activity, weight gain, sleep, psychological status, among others (16, 55–60). To compensate in part, a SEM model was thus designed to construct and model unobserved or latent dimensions and has been previously applied in periodontal research (61–65). Furthermore, this study design fails to address the possible syndemic nature of the association between periodontal inflammation and systemic state, whereby vulnerable subsets may be affected by both periodontal and other inflammatory conditions (66). Importantly, as this cross-sectional sample consisted of pregnant women classified previously as medically healthy and within a narrow age range and excluded advanced maternal age which is an independent risk factor for gestational hypertension (67), broader conclusions regarding the general populace in this region are precluded. As all subjects were recruited from those seeking care at a single tertiary center located in rural North China, selection bias may be applicable, as those reporting to small primary health care centers or those not seeking any antenatal care were not included. Thus, the present findings may be considered as the basis for further research using more robust study designs. In particular, future interventional studies investigating the effects of periodontal therapy on BP and UA are warranted in light of the present findings. Future studies should focus on shared risk factors (55–60), specific vulnerable subgroups (23) and optimal timing of intervention (68). A previous study has noted those receiving prophylactic treatment had a 7.6% incidence of low birth weight as compared to 10.1% among those not receiving any treatment (18). Considering that unexplained perinatal mortality has been linked with periodontal disease (69) and has a high prevalence in developing regions with low oral health awareness and accessibility, this preliminary data highlights that further research is essential to estimate the risk burden attributable to periodontal inflammation in mediating pregnancy complications in specific demographics. Such data would enable tailored public health measures to direct resource allocation within specific high-risk groups.

CONCLUSION

A cross-sectional study using an SEM modeling approach showed that higher periodontal inflamed surface area was associated with increased gestational blood pressure and serum uric acid in a sample of rural North Chinese pregnant women. The quantum of risk imposed by periodontal inflammation and its clinical significance in this demographic warrants investigation in more appropriately designed large-scale, longitudinal studies.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Medical Ethics Committee of Changzhi Medical College, City of Changzhi, Shanxi Province, China (No. RT2021001). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SH conceptualized the research idea, carried out data analysis, and led the paper writing. FY and HJ performed the data analysis. WS and HM were responsible for study design and data collection. SL, JZ, and HX initiated the idea of the study, supervised the project, and edited the manuscript. All authors contributed to the article and approved the submitted version.

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Assisted Reproductive Technology Outcomes in Women With Heart Disease

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Background: Women with infertility and heart disease (HD) are increasingly seeking assisted reproductive technology (ART). There is only one other study that examines the safety profile of ART in this population. This study aims to evaluate the cardiac, reproductive, and obstetric outcomes of ART in women with HD.

Methods: We conducted a retrospective case-control study of women with underlying congenital or acquired HD who underwent ART at a single University fertility center from 1/2010–3/2019. Women undergoing *in-vitro* fertilization (IVF), oocyte cryopreservation (OC) or embryo banking (EB) with HD were included. Cases were matched 3:1 with age-, cycle type- and cycle start date- matched controls without HD. Outcomes included cardiovascular (CV), reproductive, and obstetric complications during or following ART.

Results: Twenty women with HD were included. 15 (75%) had congenital HD, 1 (5%) had valvular disease, 1 (5%) had acquired cardiomyopathy, and 3 (15%) had arrhythmias. 90% were New York Heart Association class I. 55% of HD cases were modified WHO (mWHO) risk classification 1-2, 40% were mWHO 2-3 or 3, 5% were mWHO 4. Cases underwent 25 IVF, 5 OC, and 5 EB cycles and were compared with 79 controls who underwent 174 cycles. No CV complications or deaths occurred amongst cases following ART or pregnancy. There was no difference in risk of ART or obstetric outcomes amongst cases versus controls.

Conclusion: For women with HD in this small, low -risk cohort, ART posed few risks that were similar in frequency to healthy controls.

Keywords: assisted reproductive technology, *in-vitro* fertilization, congenital heart disease, modified WHO classification, maternal cardiac risk, infertility and heart disease

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INTRODUCTION

Women with cardiac disease seeking pregnancy are at increased of risk of ventricular dysfunction, arrhythmias, pre-eclampsia, *caesarean* sections, and postpartum hemorrhage (1). One in four women with cardiac disease in pregnancy are hospitalized during their pregnancy, and cardiovascular disease is the biggest indirect cause of maternal death worldwide, with an attributable rate of two deaths per 100,000 (2, 3). To better understand maternal risk, the European Society of Cardiology currently recommends utilizing the modified WHO (mWHO) classification to assess maternal risk of cardiac complications during pregnancy and recognizes that

the Cardiac Disease in Pregnancy (CAPREG) and Zwangerschap bij Aangeboren HARtAfwijkingen I (ZAHARA) scoring systems can be used to further estimate risk (3, 4). Women with heart disease at high risk of pregnancy related complications based on the above scoring systems are thus increasingly looking to assisted reproductive technology (ART) as a means to preserve their fertility (5). ART can be used to create embryos and allow high risk patients to have children through the use of a gestational carrier.

Assisted reproductive technology (ART) is becoming widely implemented worldwide. In the United States alone in 2016, there were over 86,000 ART cycles, which resulted in ∼2% of all live births (6). Although ART is becoming a more popular fertility treatment option, there are known risks involved with the process. Studies have shown that women undergoing *in-vitro* fertilization (IVF) have an increased incidence of complications, such as eclampsia, postpartum hemorrhage, and thromboembolic disease (7). In one study, investigators found that venous thromboembolism occurred in 4.2 per 1,000 women after IVF compared with 2.5 per 1,000 in women with natural pregnancies (8). One meta-analysis also found that IVF was associated with acute changes in hemodynamic parameters, with the most profound changes occurring around the days of embryonic implantation when GnRH agonist protocols are used (9). Furthermore, to obtain oocytes for ART, women must undergo controlled ovarian hyperstimulation, which can be complicated by ovarian hyperstimulation syndrome (OHSS). This phenomenon can potentially cause fluid shifts, electrolyte abnormalities, ascites, and in rare instances, pleural effusions. Oocyte retrieval also poses the risk of bleeding and anesthesia related risks (10). These complications can lead to life threatening situations, especially in women with compromised cardiac function.

While one study by Dayan et al. (11) has looked at the pregnancy outcomes and complications in women with cardiac diseases undergoing IVF, the safety of ART procedures in women with heart disease remains sparce. Thus, the current study aims to evaluate the cardiac and obstetric outcomes of ART in women with heart disease (HD) as compared to the general population.

METHODS

We conducted a retrospective case-control study of women aged 18 years and older with underlying cardiovascular disease who underwent ART at a single university fertility center between January 2010 and March 2019. Women undergoing IVF, oocyte cryopreservation (OC) or embryo banking (EB) with heart disease were included. Cases were matched 3:1 with age-, cycle type- and cycle start date- matched controls without heart disease. This study was approved by the Institutional Review Board of New York University Langone Health. Consent was obtained at the time of treatment.

Patients were classified as having either acquired or congenital heart disease (CHD). Acquired heart disease was further categorized as valvular disease, arrhythmia, cardiomyopathy, and ischemic heart disease. Cases were categorized based on maternal risk using the mWHO criteria, in which WHO class I is associated with very low risk of maternal cardiac events (2.5–5%), class II are low-moderate risk (5.7–10.5%), WHO II–III are moderate risk (10–19%), WHO III are at high risk (19–27%), and WHO IV (40–100%) in which women should be advised against pregnancy (4).

Primary outcomes included cardiovascular (CV) complications during or following ART (arrhythmias, heart failure, hypotension, thrombosis, or CV death), reproductive complications, and obstetric complications. Secondary outcomes included obstetric outcomes and neonatal outcomes and complications. Statistical analysis was conducted using SPSS. Two tailed paired *t*-tests were conducted to calculate statistical significance.

TABLE 1 | Baseline characteristics of women with HD and controls.

	Women with HD* ($N = 20$)	Control patients ($N = 79$)	*P*-Value
Age (years), mean (STD)	35.8 (±5.3)	34.7 (±4.9)	$P = 0.43$
Race			
Caucasian	17 (85%)	50 (63%)	
Asian/Indian	2 (10%)	12 (15%)	
African	0 (0%)	1(1%)	
Other	0 (0%)	4 (5%)	
Unknown	1 (5%)	12 (15%)	
Ethnicity			
Hispanic	0 (0%)	3 (4%)	
Comorbidities			
Hypertension (%)	1 (5%)	1 (1%)	$P = 0.36$
Diabetes Mellitus (%)	2 (10%)	1 (1%)	$P = 0.10$
Stroke (%)	1 (5%)	0 (0%)	$P = 0.20$
Chronic Kidney Disease (%)	1 (5%)	0 (0%)	$P = 0.20$
Hypothyroidism (%)	1 (5%)	7 (9%)	$P = 0.69$
Obesity (BMI > 30) (%)	0 (0%)	2 (3%)	$P = 1$
Polycystic Ovarian Syndrome (%)	1 (5%)	8 (10%)	$P = 0.68$

HD, heart disease.

RESULTS

Twenty cases underwent a total of 25 IVF cycles, 5 oocyte cryopreservation cycles, and 5 embryo banking cycles, whereas 79 controls had total of 174. Average age of cases was 35.8 ± 5.3 years, which was similar to that of controls with an average age of 34.7 ± 4.9 years. The majority of cases ($N = 17$, 85%) and controls ($N = 50$, 63%) were Caucasian. There was no significant difference in co-morbidities between the two groups. The most common co-morbidity among cases was diabetes mellitus ($N = 2$, 10%). The most common co-morbidity among controls was polycystic ovarian syndrome ($N = 8$, 10%) (**Table 1**). 11 (55%) cases and 39 (49%) controls were nulliparous at the start of ART.

Of 20 cases, 15 (75%) had CHD, 1 (5%) had acquired valvular disease, 1 (5%) had acquired cardiomyopathy, and 3 (15%) had arrhythmias. Further breakdown of the type of HD is shown

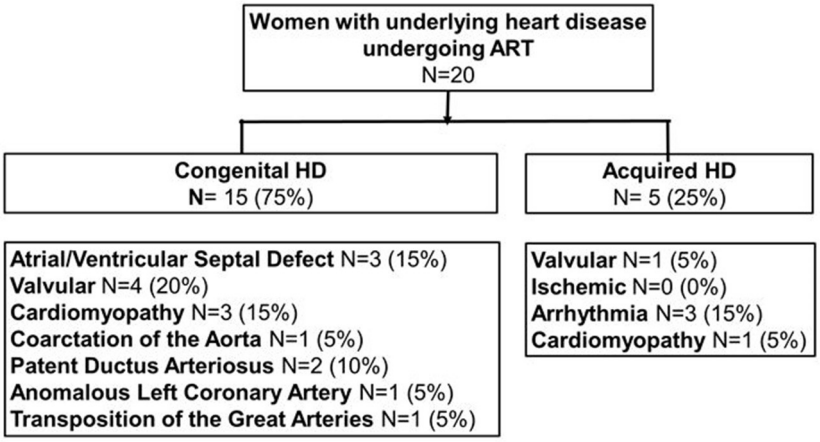

FIGURE 1 | Classification of subjects with heart disease into acquired ($N = 5$) and congenital heart disease ($N = 15$). ART, assisted reproductive technology; HD, heart disease.

TABLE 2 | Cardiovascular and ART complications of women with HD and controls.

	ART* cycles in women with HD† ($N = 35$)	Control ART cycles in controls ($N = 174$)
Cardiac outcome		
Arrhythmia (%)	0 (0%)	0 (0%)
Thrombosis (%)	0 (0%)	1 (1%)
Hypotension (%)	0 (0%)	1 (1%)
Heart failure (%)	0 (0%)	0 (0%)
Cardiac death (%)	0 (0%)	0 (0%)
ART outcome		
Bleeding during ovum retrieval (%)	0 (0%)	0 (0%)
OHSS‡ (%)	1 (3%)	8 (5%)
Syncope (%)	1 (3%)	1 (1%)

*ART, assisted reproductive technology.
† HD, heart disease.
‡OHSS, ovarian hyperstimulation syndrome.

in **Figure 1**. The majority of cases ($N = 6$, 30%) were mWHO class II. 5 (25%) cases were mWHO class I, 3 (15%) were mWHO class II-III, 5 (25%) were mWHO class III, and 1 (5%) was mWHO class IV. Ninety percentage of cases were New York Heart Association (NYHA) class I at the time of ART. To proceed with ART therapy, all patients had to be candidates for outpatient sedation.

The mWHO class III patients consisted of a case of non-compaction cardiomyopathy with a normal ejection fraction (EF), a case of anomalous left coronary artery who underwent bypass surgery, a case of dextro-transposition of the great arteries who underwent the Blalock-Hanlon procedure and arterial switch procedure with a mechanical aortic valve, a case of dilated cardiomyopathy with a reduce EF of 35–40%, and a case of hypertrophic cardiomyopathy who had undergone myomectomy and eventually heart transplant. The mWHO class IV patient was a case of peripartum cardiomyopathy with an EF of 25–30%. Three cycles (one mWHO class IV and 2 mWHO class III) utilized gestational carriers.

Among cases, there were no CV complications during or after ART cycle. Among controls, 1 (1%) cycle was complicated by stroke after ART cycle and 1 (1%) cycle was complicated by hypotension during the ART cycle. No death occurred in either group as a result of ART. The most common ART complication in both groups was ovarian hyperstimulation syndrome (OHSS) with 1 (3%) cycle in cases and 8 (5%) cycles in controls. The incidence of cardiovascular and ART complications was similar amongst cases vs. controls (**Table 2**).

For obstetric outcomes, 8 (32%) IVF cycles resulted in pregnancy in cases compared to 69 (46%) IVF cycles among controls. For those who became pregnant among cases, 6 (24%) cycles resulted in single gestation, 0 in multiple gestation, 1 (4%) in spontaneous abortion, and 1 (4%) in ectopic pregnancy. There were no pre-term pregnancies among cases. For controls, 47 (31%) cycles resulted in single gestation, 4 (3%) in multiple gestation, and 18 (12%) in spontaneous abortion. There were no ectopic pregnancies. 8 (12%) of control pregnancies were pre-term.

Among cases, 1 (13%) pregnancy was complicated by pre-eclampsia, and 1 (13%) was complicated by antepartum bleeding. In controls, 9 (13%) pregnancies were complicated by pre-eclampsia, 4 (6%) by gestational diabetes, and 1 (1%) by postpartum hemorrhage. No death occurred in either group as a result of pregnancy. The incidence of obstetric outcomes and complications were similar amongst cases vs. controls (**Table 3**). In addition, there were no neonatal complications amongst the cases. There was one incidence of a congenital abnormality amongst a control.

TABLE 3 | Obstetric outcomes and complications of women with HD and controls.

	Pregnancy in women with HD* (*N* = 8)	Control pregnancies (*N* = 79)
Obstetric outcome		
Single gestation (%)	6 (75%)	47 (68%)
Multiple gestation (%)	0 (0%)	4 (6%)
Spontaneous abortion (%)	1 (13%)	18 (26%)
Ectopic pregnancy (%)	1 (13%)	0 (0%)
Obstetric complications		
Maternal non-cardiac death (%)	0 (0%)	0 (0%)
Antepartum hemorrhage (%)	1 (13%)	0 (0%)
Post-partum hemorrhage (%)	0 (0%)	1 (1%)
Pre-eclampsia (%)	1 (13%)	9 (13%)
Gestational diabetes (%)	0 (0%)	4 (6%)

HD, heart disease.

DISCUSSION

This study demonstrates that in our cohort of women with acquired or underlying congenital HD, ART has a safety profile that is similar in frequency to healthy controls with no history of cardiac disease. Similar to studies that examined ART in the general population, OHSS was a significant ART complication (12). The British Royal College of Obstetricians and Gynecologists cites an incidence for mild OHSS of about one in every three cycles of IVF and an incidence for moderate or severe forms ranging from 3.1 to 8% of cycles (13). This is similar to the incidence in our cohort. However, a study by Dayan et al., which explored a similar population to ours, found an increased incidence of OHSS (18% vs. 1%) when compared to a population-based study (11).

For pregnancy and neonatal outcomes, our cohort demonstrated lower incidence of complications than other studies. The aforementioned study by Dayan et al., for example, noted an increased incidence of maternal cardiovascular complications (27% vs. 13%), and neonatal complications (45% vs. 20%) in women with HD when compared to a population-based study (11). A systematic review of 50 cohort studies by Qin et al. also demonstrated significantly increased maternal risk outcomes associated with ART that were not seen in our population, such as placenta previa (271% increase) and perinatal mortality (64% increase) (14).

Several factors can possibly account for these differences. First, this study documented a greater number of ART cycles, and the aforementioned Dayan et al. study documented only self-reported complications. That study also did not have a control group. Moreover, ART is a relatively safe practice. In one study of 23,827 transvaginal oocyte retrieval procedures, <1% of patients suffered complications with anesthesia complications comprising only 0.06% (15). Our sample size may have been too small to demonstrate the increased risk of ART complications.

An important factor also lies in the differences between the studied cohorts. The vast majority of our cases were NYHA functional class I and had to be considered low risk enough to receive outpatient sedation for the ART procedure. The Dayan et al. study only investigated cases that resulted in pregnancy rather than all cycles. Pregnancies in women with heart disease have previously been shown to be associated with cardiac events, which could account for that study's increased incidence in cardiac complications (16, 17). Also, there were no cases of multiple gestations in the HD group in our study, a higher risk pregnancy, which may have led to underestimation of risk. Furthermore, two patients of the HD group were deemed to be high-risk and used gestational carriers, which offset the risk of pregnancy complications. Due to this risk stratification, our lower risk cohort may not be representative of majority high risk cohorts.

Overall reduction of complications seen in women with HD undergoing ART can also be attributed to both improved care of patients with HD and advancements in ART. Awareness of the medical complexity of patients with CHD, for example, has led to specialty clinics and specific guidelines for transition of care from childhood into adulthood (18, 19). Different aspects of ART treatment can also be adjusted for patients at increased risk. The IVF protocol, for example, can be altered to a GNRH antagonist-based protocol to reduce the risk of OHSS while maintaining a similar pregnancy rate (20). Physicians have also identified potentially hemodynamically compromising investigations conducted during fertility investigations, such as hysterosalpingograms. While this test is benign in most patients, pain and cervical manipulation can result in a vagal response, which can be potentially dangerous in women with pulmonary hypertension or a Fontan repair (21). This complication can be prevented by implementing cardiovascular monitoring and providing adequate pain relief with either a paracervical block or systemic opioids (22, 23). If patients remain at high-risk despite precautions, physicians are aware to recommend gestational carriers.

Advancements in embryo culture and cryopreservation techniques and the establishment of embryo transfer guidelines have also reduced the risk of OHSS, multiple gestations, and their associated complications (24). The reduction in the number of embryos transferred and the use of pre-implementation genetic testing for aneuploidy may account for the absence of multiple gestations seen in our cases. The success of these techniques speaks toward the possibility for a standardized ART protocol for women with HD to ensure reduction of cardiovascular and obstetric complications.

This study is limited by its retrospective design, single center analysis, and small sample size. Our study also did not include any patients with ischemic heart disease, a subgroup of women that deserves further study. Importantly, our cohort did not include any patients of African American or Hispanic ethnicity so the results cannot be extended to these populations. Additionally, our study is limited in the timeline of our analysis. We do not have data on follow-up beyond the immediate post-partum period, so findings do not account for the possibility of long-term cardiac complications as a result of ART (25).

This study found that for women with primarily low risk HD, ART does not pose any more cardiac, reproductive, or obstetric risk when compared to healthy age- and cycle- matched controls. Given our limited scope, further studies with a more ethnically diverse cohort are needed to confirm the short-term and long-term safety of ART in patients with various types of cardiac disease and to evaluate the success rate of ART in this population. With this information, physicians referring women with cardiac disease for ART may be better suited to counsel their patients on fertility treatment options and their procedural risks.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by New York University Langone Health. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

SM and CW contributed to conception and design of the study. SM and MQ collected and organized the data. AH performed the statistical analysis. MQ and AH wrote sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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Predictors of Maternal Death Among Women With Pulmonary Hypertension in China From 2012 to 2020: A Retrospective Single-Center Study

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Background: Previous studies have suggested that pregnant women with pulmonary hypertension (PH) have high maternal mortality. However, indexes or factors that can predict maternal death are lacking.

Methods: We retrospectively reviewed pregnant women with PH admitted for delivery from 2012 to 2020 and followed them for over 6 months. The patients were divided into two groups according to 10-day survival status after delivery. Predictive models and predictors for maternal death were identified using four machine learning algorithms: naïve Bayes, random forest, gradient boosting decision tree (GBDT), and support vector machine.

Results: A total of 299 patients were included. The most frequent PH classifications were Group 1 PH (73.9%) and Group 2 PH (23.7%). The mortality within 10 days after delivery was 9.4% and higher in Group 1 PH than in the other PH groups (11.7 vs. 2.6%, $P = 0.016$). We identified 17 predictors, each with a P-value < 0.05 by univariable analysis, that were associated with an increased risk of death, and the most notable were pulmonary artery systolic pressure (PASP), platelet count, red cell distribution width, N-terminal brain natriuretic peptide (NT-proBNP), and albumin (all $P < 0.01$). Four prediction models were established using the candidate variables, and the GBDT model showed the best performance (F1-score = 66.7%, area under the curve = 0.93). Feature importance showed that the three most important predictors were NT-proBNP, PASP, and albumin.

Conclusion: Mortality remained high, particularly in Group 1 PH. Our study shows that NT-proBNP, PASP, and albumin are the most important predictors of maternal death in the GBDT model. These findings may help clinicians provide better advice regarding fertility for women with PH.

Keywords: maternal death, predictor, pregnancy, pulmonary hypertension, feature importance

INTRODUCTION

Pulmonary hypertension (PH) is a pathophysiological disorder characterized by proliferation, narrowing, and remolding of the pulmonary vasculature and can complicate respiratory and cardiovascular diseases, which lead to right heart failure and premature death (1). The estimated 5-year survival rate is 72% in highly functioning patients and as low as 28% for those presenting with advanced symptoms (2).

Compared to men, women are two to four times more common to develop PH (3, 4). Moreover, women affected by PH are often young and in their childbearing age (4, 5). The maternal mortality rate for PH in pregnancy is known to be high (16–30%) (6). That is largely because of extensive physiological changes during pregnancy, such as an increase in intravascular volume, red cell mass, coagulability, oxygen consumption, cardiac output and a decrease in systemic vascular resistance, which may contribute to right ventricular failure (7). Most deaths occur during delivery or within 10 days after delivery, mainly due to right heart failure and cardiovascular collapse (4, 8–10). Therefore, the current guidelines recommend that pregnancy should be avoided in women with PH, especially those with pulmonary arterial hypertension (PAH) (1, 4, 6). However, some women develop this condition during pregnancy. In addition, socioeconomic, religious, or cultural factors drive some women with PH to desire to have a child. For these reasons, they decide to become pregnant or continue with an unplanned pregnancy (4, 8).

To date, due to limitations involving small sample sizes for statistical comparisons in previous studies, the risk factors for maternal death in pregnancy with PH remain unclear (8, 9, 11, 12).

Therefore, an in-depth understanding of the risk factors may help to identify high-risk pregnancy and provide appropriate medical advice, including pre-pregnancy counseling, and optimal management during pregnancy, which would be particular useful for women with mild PH. Hence, in the present study, we aimed to analyze pregnancy outcomes, establish death-related predictive models, and screen death-related predictors among pregnant women with PH.

MATERIALS AND METHODS

Study Patients

From June 2012 to December 2020, we retrospectively reviewed women with PH admitted for delivery in our hospital. Patients less than 18 years old, lacking necessary data (e.g., echocardiography, World Health Organization functional class), or with elevated right ventricular systolic pressure caused by outflow tract obstruction/pulmonary stenosis were excluded (**Figure 1**).

The diagnostic criterion for PH was a mean pulmonary arterial pressure $\geq$ 25 mmHg at rest measured by right heart catheterization (RHC) (1). In addition, if RHC was not available for the echocardiographic criteria for intermediate or high probability of PH, tricuspid regurgitation velocity $>$ 2.8 m/s or tricuspid regurgitation velocity $\leq$ 2.8 m/s combined with at least two different categories of other echocardiographic signs (detail criteria see **Supplementary Table 1**) was also acceptable in the present study (1). A pregnancy loss occurring before 24 weeks of gestation was defined as abortion (13).

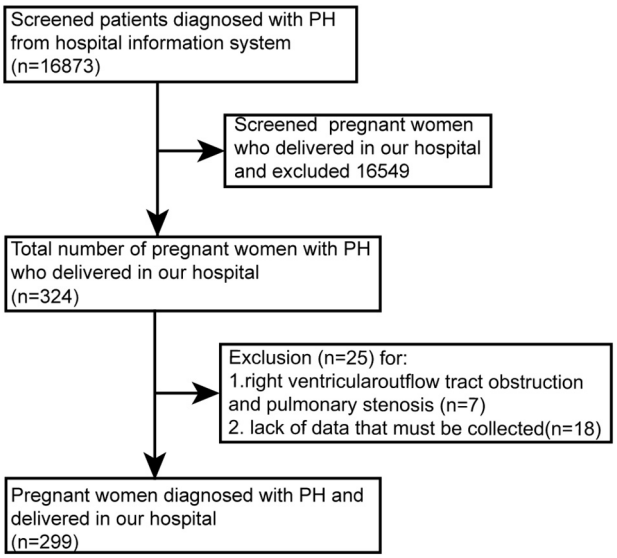

FIGURE 1 | Patient flow chart. PH, pulmonary hypertension.

Data Collection

We collected data from the Hospital Information System. Baseline data included demographic characteristics, diagnostic methods, diagnostic time, prior medical status, pregnancy history, gestational age, and PH etiology. Additionally, data on management and pregnancy outcomes, including delivery mode, anesthesia method, neonatal sex, birth weight, medication after delivery, and maternal or fetal vital status, were collected. Furthermore, the following risk factors and outcome predictors reported for PH and pregnancy in previous studies were collected, including the presence or absence of clinical signs of right heart failure, the progression of symptoms, syncope, World Health Organization (WHO) functional class, right atrium (RA) area, pericardial effusion, Eisenmenger syndrome, pulmonary artery systolic pressure (PASP), complications (e.g., peripartum cardiomyopathy, preeclampsia, diabetes mellitus), and laboratory parameters such as platelet count, red cell distribution width (RDW), lymphocyte count, neutrophil-to-leukocyte ratio, N-terminal brain natriuretic peptide (NT-proBNP), prothrombin time (PT), activated partial thromboplastin time (APTT), thrombin time, plasma fibrinogen, creatinine, blood urea nitrogen (BUN), uric acid, serum albumin, and globulin (1, 4, 5, 14–17). The clinical features of right heart failure, WHO functional class and progression of symptoms were defined according to the guidelines (1). The RA area, pericardial effusion, presence of Eisenmenger syndrome, and PASP were measured by echocardiography. All collected data from laboratory measurements and echocardiography were

evaluated within 1 week before delivery in our center. Survival status was obtained by hospital records or telephone interviews. Based on the survival status within 10 days after delivery, patients were divided into two groups (survivors and non-survivors).

Statistical Analysis

Univariable analysis: (a) Normally distributed continuous variables are presented as the mean ± *SD* (standard deviation) and were analyzed using Student's *t*-test. (b) Non-normally distributed variables are presented as the median with the first and third quartiles: M (Q1, Q3) and were analyzed by Mann-Whitney *U*-tests. (c) Categorical variables are presented as numbers and percentages, and comparisons of groups were performed using Pearson's chi-square tests with a theoretical frequency ≥ 5. (d) Continuity adjusted chi-square tests were used for theoretical frequency ≥ 1 but < 5. (e) Fisher's exact tests were used for theoretical frequency < 1. The above statistical analyses were performed using IBM SPSS version 25.

Four machine learning (ML) algorithms—random forest (RF), naïve Bayes (NB), gradient boosting decision tree (GBDT), and support vector machine (SVM)—were employed to establish death-related prediction models and detect critical predictors in the present study. In some real-world studies, the classified data might have a bias because of class imbalance. Some outcomes as minority classes for binary classification were rare events, while other outcomes referred to as majority classes were commonly occurring events (18). The imbalance ratio (the ratio of the minority class size to the majority class size) of the datasets was above10:1, which could be regarded as a highly imbalanced dataset (18). This issue would decrease the predictive performance of the classifiers in machine learning (18). The proportions of survivors (90.6%) and non-survivors (9.4%) were also imbalanced in our study. The synthetic minority oversampling technique (SMOTE) algorithm employed in our study, which generates minority samples in the training dataset before training, is one of the best-known oversampling techniques, is most commonly applied to handle class imbalance problems and improve the predictive performance of models (18). Variables with $P < 0.05$ in the univariable analyses were included in the models. With the random state, the original dataset was randomly divided into a training dataset and a test dataset at a ratio of 8:2.

Evaluation of the model's stability and parameter tuning were performed *via* an internal K-fold cross-validation ($k = 5$) in the training set after SMOTE. We adopted the accuracy, recall, precision, fuzzy measure (F1-score), and area under the curve (AUC) and mainly used the AUC and F1-score of the independent tested dataset to evaluate the performance of the models (19). Precision = $\frac{TP}{TP+FP}$, Recall = Sensitivity = $\frac{TP}{TP+FN}$, Accuracy = $\frac{TP+TN}{P+N}$ (TP: true positives, FP: false positives, FN: false negatives, P: positives, N: negatives). The F1-score is a weighted harmonic means of precision and recall. Feature importance for the best-performing model was reported to screen key predictors (20). The ranking of feature importance is based on information gain, which is employed to evaluate the additional information provided by each feature to the classifiers. Building and assessment of the prediction model, SMOTE, of the training dataset was performed with Python 3.6 (Python Software Foundation) using the scikit-learn library. Furthermore, the cut-off levels of significant predictors to predict death among pregnant women with PH could be found based on the receiver operating characteristic (ROC) curve using IBM SPSS version 25.

RESULTS

General Demographic and Clinical Characteristics

This study included 299 patients (**Figure 1**). PH was diagnosed in 27 (9.0%) patients by RHC. The other 272 (81.0%) cases were diagnosed by echocardiography, of which 41 (13.7%) cases had RHC for reconfirmation after delivery, mostly during congenital heart disease surgery. Sixty-six patients (22.1%) were diagnosed before pregnancy, while 233 patients (77.9%) were newly diagnosed during pregnancy. Among the 233 cases, some developed PH only during pregnancy because the pre-pregnancy check-ups did not identify PH, the other did not know that PH was present before pregnancy.

The median age of the 299 patients was 28 years (Q1–Q3 = 25.0–31.0). The median gestational age was 35.6 weeks (Q1–Q3 = 29.7–38.1). The median PASP was 57.0 mmHg (Q1–Q3 = 42.0–87.0). One hundred fifty-one (51.8%) of them were nulliparous. Further classification of the 299 cases showed that 221 cases (73.9%) displayed Group 1 PH (PAH). Of these women, 24 (10.9%) had idiopathic PAH. Nineteen women (8.6%) had connective tissue disease-associated pulmonary arterial hypertension. One hundred seventy-eight patients (80.5%) had congenital heart disease associated with pulmonary arterial hypertension (atrial septal defect, $n = 81$; ventricle septal defect, n = 79; patent ductus arteriosus, n = 15; tetralogy of Fallot, $n = 3$). Seventy-one (23.7%) patients had Group 2 PH (due to left heart disease), with rheumatic heart disease in 39 (13.0%) women and cardiopathy in 32 (10.7%) women. Three patients (1.0%) had Group 3 PH (due to lung disease and/or hypoxia), and four (1.3%) patients had Group 5 PH (with unclear and/or multifactorial mechanisms).

Among these cases, 17 (5.7%) patients had twin pregnancies, and 47 (15.7%) patients (less than 24 weeks of gestation) underwent assisted abortion, including therapeutic abortion, curettage and cesarean section. The patients gave birth to a total of 259 neonates, of which 82 (31.7%) had birth weights below 2,500 g, and 30 (11.6%) died during the neonatal period. Thirty (11.6%) fetal or neonatal deaths up to 10 days after delivery occurred in 26 (8.7%) pregnancies, including 4 (1.3%) twin pregnancies. Additional clinical characteristics are presented in **Table 1**.

Maternal Mortality and Characteristics of the Survivors and Non-survivors

Twenty-eight (9.4%) women died within 10 days after delivery. The median time of death was 1 day after delivery (ranging from during delivery to 8 days). Of the patients who died, 27 died of

TABLE 1 | Comparison of demographic and clinical characteristics between the survivor and non-survivor groups.

	Total patient (*n* = 299)	Survivors (*n* = 271)	Non-survivors (*n* = 28)	t/z/χ^2	*P**
Characteristics before delivery					
Age (years)	28.0 (25.0, 31.0)	28.0 (25.0, 31.0)	28.0 (24.0, 31.0)	-0.642	0.521
Gestational age (weeks)	35.6 (29.7, 38.1)	35.9 (29.7, 38.1)	31.9 (28.7, 36.7)	-2.025	0.043
PH diagnosis before pregnancy, *n* (%)	66 (22.1)	57 (21.0)	9 (32.1%)	1.821	0.177
Nulliparous, *n* (%)	155 (51.8)	140 (51.7)	15 (53.6)	0.037	0.847
Clinical classification of PH, *n* (%)				5.750	0.016†
Group 1	221 (73.9)	195 (72.0)	26 (92.9)		
IPAH	24 (8.0)	20 (7.4)	4 (14.3)		
CTD-PAH	19 (6.4)	17 (6.3)	2 (7.1)		
CHD-PAH	178 (59.5)	158 (58.3)	20 (71.4)		
Other groups of PH	78 (26.1)	76 (28.0)	2 (7.1)		
Group 2	71 (23.7)	69 (25.5)	2 (7.1)		
Group 3	3 (1.0)	3 (1.1)	0 (0.0)		
Group 5	4 (1.3)	4 (1.5)	0 (0.0)		
Right heart failure, *n* (%)	70 (23.4)	55 (20.3)	15 (53.6)	15.672	0.001
Progression of symptoms, *n* (%)	156 (52.2)	134 (49.4)	22 (78.6)	8.627	0.003
WHO functional class, *n* (%)				24.582	0.001
I, II	150 (50.2)	145 (53.5)	5 (17.9)		
III	96 (32.1)	87 (32.1)	9 (32.1)		
IV	53 (17.7)	39 (14.4)	14 (50.0)		
Pericardial effusion, *n* (%)	48 (16.1)	43 (15.9)	5 (17.9)	0.075	0.785
RA area (cm^2)	19.5 (14.7, 25.0)	19.4 (14.5, 24.6)	22.5 (18.9, 28.2)	-2.777	0.005
PASP (mm Hg)	57.0 (42.0, 87.0)	55.0 (41.0, 80.0)	95.5 (76.0, 111.5)	-5.005	0.001
Disease-targeted therapies during pregnancy‡, *n* (%)	20 (9.0)	17 (8.7)	3 (11.5)	0.014	0.905
Comorbidity, *n* (%)	68 (22.7)	65 (24.0)	3 (10.7)	2.544	0.111
Eisenmenger syndrome, *n* (%)	47 (15.7)	38 (14.0)	9 (32.1)	4.997	0.025
Platelet count ($10^3/\mu L$)	184.8 ± 75.1	191.2 ± 71.9	120.4 ± 76.0	-4.957	0.001
Lymphocyte count ($10^3/\mu L$)	1.5 (1.2, 1.9)	1.5 (1.2, 1.9)	1.5 (1.2, 1.9)	0.169	0.866
Neutrophil-to-leukocyte ratio	4.2 (3.2, 6.0)	4.1 (3.1, 5.8)	4.9 (3.3, 7.8)	-1.743	0.081
RDW (%)	14.5 (13.7, 16.6)	14.4 (13.6, 16.5)	15.5 (14.5, 17.0)	-2.595	0.009
NT-proBNP (pg/mL)	366.2 (122.9, 1165.8)	314.1 (103.3, 1165.8)	2255.0 (786.2, 3619.0)	-5.105	0.001
Thrombin time (s)	13.9 (12.9, 15.2)	13.9 (12.9, 15.3)	13.9 (13.0, 15.2)	-0.242	0.809
PT (s)	9.8 (9.2, 10.5)	9.7 (9.2, 10.4)	10.3 (9.8, 11.5)	-2.943	0.003
APTT (s)	29.3 (27.2, 32.4)	29.3 (27.1, 32.2)	31.2 (29.3, 34.6)	-2.472	0.013
Fibrinogen (g/L)	3.5 ± 0.8	3.5 ± 0.8	3.3 ± 1.0	-1.357	0.176
Creatinine (μmol/L)	49.0 (42.3, 61.0)	49.0 (42.0, 60.0)	53.5 (46.3, 71.8)	-1.867	0.062
BUN (mmol/L)	3.8 (3.1, 4.9)	3.8 (3.0, 4.8)	5.0 (3.5, 7.4)	-2.998	0.003
Uric acid (μmol/L)	328.0 (255.0, 423.0)	323.0 (253.0, 414.0)	426.0 (330.0, 576.5)	-3.435	0.001
Albumin (g/L)	32.6 ± 4.9	32.9 ± 4.8	30.3 ± 5.2	-2.681	0.007
Globulin (g/L)	29.5 (26.7, 32.4)	29.5 (26.6, 32.3)	29.6 (27.1, 33.0)	-0.497	0.619
Management					
Abortion, *n* (%)	47 (15.7)	42 (15.5)	5 (17.9)	0.003	0.957
Anesthesia methods				9.922	0.007
General anesthesia, *n* (%)	115 (38.5)	97 (35.8)	18 (64.3)		
Neuroaxonal anesthesia, *n* (%)	156 (52.2)	149 (49.8)	7 (25.0)		
No anesthesia	28 (9.4)	25 (9.2)	3 (10.7)		
Vaginal delivery, *n* (%)	53 (17.7)	47 (17.3)	6 (21.4)	0.078	0.780
Disease-targeted therapies after delivery‡, *n* (%)	65 (29.4.)	55 (20.3)	10 (35.7)	1.162	0.281

**P-value of the difference between the survivor group and the non-survivor group, †P-value for Group 1 and other groups, ‡not applicable in 78 cases of other group PH. PH, pulmonary hypertension; IPAH, idiopathic pulmonary arterial hypertension; CTD-PAH, connective tissue disease-associated pulmonary arterial hypertension; WHO, World Health Organization; RA, right atrium; PASP, pulmonary artery systolic pressure; RDW, red cell distribution width; NT-proBNP, N-terminal brain natriuretic peptide; PT, prothrombin time; APTT, activated partial thromboplastin time; BUN, blood urea nitrogen.*

heart failure, and one died of postpartum hemorrhage. Sixteen neonates with a gestational age over 24 weeks survived among 23 cases with maternal deaths. Three (1.3%) of the 233 patients died within 6 months after delivery (one at 1 month, one at 3 months, and another at 5 months after delivery). Two (0.7%) patients had syncope, and 20 (6.7%) patients took anticoagulants before delivery. Information on the management of the PH patients is presented in **Table 1**.

The median gestational age of the survivor group was 35.9 weeks (Q1–Q3 = 29.7–38.1), and the mean gestational age of the non-survivor group was 31.9 weeks (Q1–Q3 = 28.7–36.7). We found that the mortality was higher for the women with Group 1 PH (26 of 221 cases, 11.7%) than for those with other types of PH (2 of 78 cases, 2.6%) ($P = 0.016$). The mortality rate differed significantly between women with and without Eisenmenger syndrome [19.1% (9 of 47 cases) vs. 7.5% (19 of 252 cases), $P = 0.025$]. Compared to the survivor group, the non-survivor group had a worse WHO functional class (I, II class: 17.9% vs. 53.5% and IV class: 50.0% vs. 14.4%, $P = 0.001$). The incidences of right heart failure (53.6% vs. 20.3%, $P = 0.001$) and progression of symptoms (78.6% vs. 49.4%, $P = 0.003$) were higher in the non-survivor group than in the survivor group. Patients in the non-survivor group had a larger RA area [23.9 ± 6.9 cm^2 vs. 19.4 (14.5, 24.6) cm^2, $P = 0.005$], higher PASP [92.7 ± 8.0 mmHg vs. 55.0 (41.0, 80.0) mmHg, $P = 0.001$], lower platelet count [$(120.4 \pm 76.0) \times 10^3/\mu$L vs. $(191.2 \pm 71.9) \times 10^3/\mu$L, $P = 0.001$], higher RDW [15.5% (14.5, 17.0) vs. 14.4% (13.6, 16.5), $P = 0.009$], higher NT-proBNP [2255.0 (786.2, 3619.0) pg/ml vs. 314.1 (103.3, 1165.8) pg/mL, $P = 0.001$], longer PT [10.3 (9.8, 11.5) s vs. 9.7 (9.2, 10.4) s, $P = 0.003$], longer APTT [31.2 (29.3, 34.6) s vs. 29.3 (27.1, 32.2) s, $P = 0.013$], higher BUN [5.5 ± 2.4 mmol/L vs. 3.8 (3.0, 4.9) mmol/L, $P = 0.029$] and higher uric acid [$439.7 \pm 142.5\mu$mol/L vs. 323.0 μmol/L (253.0, 414.0), $P = 0.001$], and lower ALB (30.3 ± 4.3 g/L vs. 33.1 ± 5.0 g/L, $P = 0.039$) than the patients in the survivor group. In a comparison of neuroaxonal anesthesia and no anesthesia, women under general anesthesia had the highest mortality (18/115, 15.7%), ($P = 0.007$) (**Table 1**).

Performance and Feature Importance of Prediction Models

With the random state, the original dataset was randomly divided into a training dataset and a test dataset at a ratio of 8:2. ($n = 239$ in the training dataset, $n = 60$ cases in the test dataset). With the SMOTE, the training dataset samples increased to 434 (217 cases in the survivor group and 217 cases in the non-survivor group). In the test dataset, 54 cases were in the survivor group, and 6 cases were in the non-survivor group.

Feature selection was based on a P-value < 0.05 in univariable analyses. Fivefold cross-validation was performed on the training dataset after SMOTE. After parameter tuning in fivefold cross-validation, we built four prediction models based on the total training dataset by machine learning algorithms. **Table 2** shows the comparisons of different algorithms for the cross-validation and the training group.

For the test dataset, the F1-score, precision, accuracy, recall, and AUC values of the models are outlined in **Table 2**. The GBDT model obtained the highest F1-score (66.7%), precision (100.0%), and accuracy (95.0%), with the second-highest recall (50.0%) and AUC (0.93). Therefore, the GBDT model performed best in this study.

The correlations between the variables are shown in **Supplementary Figure 1**. The WHO functional class was moderately and positively correlated with right heart failure and progression of symptoms, and BUN was moderately and positively correlated with uric acid (all $r > 0.5$, $P < 0.05$). Each variable's feature importance from the GBDT model showed that the top three most critical predictive variables were

TABLE 2 | Model performance of the training and test datasets.

	Precision (%)	Recall (%)	Accuracy (%)	F1-score (%)	AUC
Cross-validation set					
NB	85.2	62.3	75.1	71.2	0.77
GBDT	95.2	100.0	97.5	97.5	1.00
SVM	81.8	70.7	77.7	75.7	0.81
RF	97.1	100.0	98.40	98.5	1.00
Training set					
NB	84.6	60.8	74.9	70.8	0.76
GBDT	100.0	100.0	100.0	100.0	1.00
SVM	83.8	73.7	79.7	78.4	0.83
RF	100.0	100.0	100.0	100.0	1.00
Test set					
NB	33.3	33.3	86.7	33.3	0.83
GBDT	100.0	50.0	95.0	66.7	0.93
SVM	57.1	66.7	91.7	61.5	0.90
RF	75.0	50.0	93.3	60.0	0.94

AUC, area under the curve; NB, naïve Bayes; GBDT, gradient boosting decision tree; SVM, support vector machine; RF, random forest.

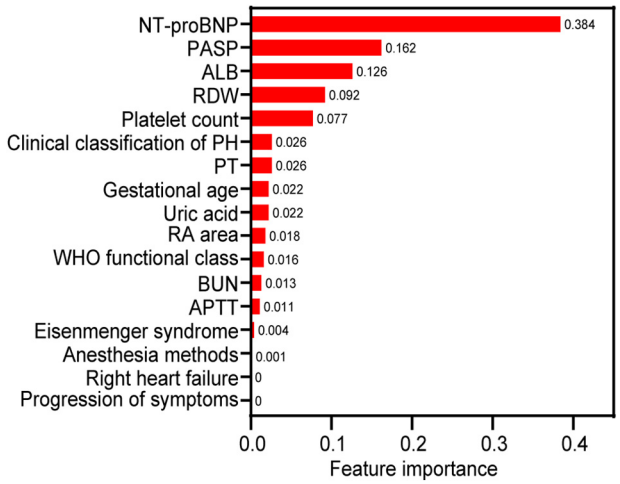

FIGURE 2 | The relative feature importance of predictor variables included in the gradient boosting decision tree for predicting the death of pregnant women with pulmonary hypertension. NT-proBNP, N-terminal brain natriuretic peptide; PASP, pulmonary artery systolic pressure; ALB, albumin; RA, right atrium; APTT, activated partial thromboplastin time; RDW, red cell distribution width; PT, prothrombin time; WHO, World Health Organization.

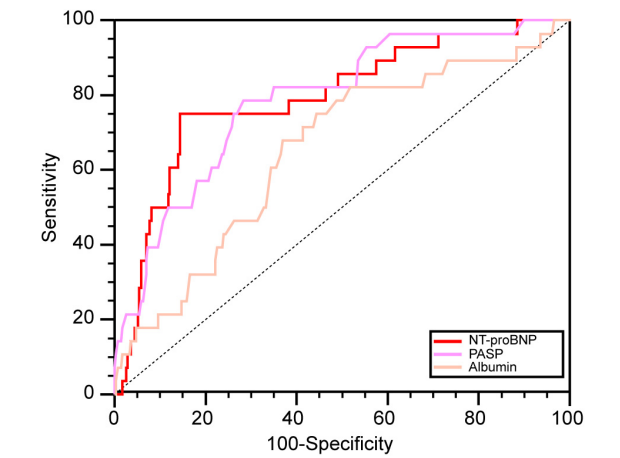

FIGURE 3 | The ROC curves of significant predictors. NT-proBNP, N-terminal brain natriuretic peptide; PASP, pulmonary artery systolic pressure; ALB, albumin.

NT-proBNP, PASP, and ALB, and is shown in **Figure 2** after normalization processing (score for each feature importance $= \frac{\text{the raw score for each feature importance}}{\text{the sum of all raw scores for features importance}}$). The order of feature importance across fivefold cross-validation runs was also analyzed, and this was stable and similar (**Supplementary Table 2**). The ranking of feature importance is based on information gain, which is employed to evaluate the additional information provided by each feature to the classifiers.

The areas under the ROC curves for NT-proBNP, PASP, and ALB to predict death in pregnant women with PH were 0.793, 0.787, and 0.654, respectively (all $P < 0.05$) (**Figure 3**). Based on the Youden index, the optimal cut-off values of NT-proBNP, PASP, and ALB were 1519.3 pg/mL, 74.0 mmHg, and 31.7 g/L, with sensitivity and specificity values of 75.0 and 85.6%, 78.6 and 71.6%, and 67.9 and 63.1%, respectively.

DISCUSSION

Our study has a unique large sample, focusing on pregnancy outcomes and including 299 pregnant women with PH, compared to other studies (5, 8, 10, 11). This is a scarce original study that sought to identify predictors for maternal death in pregnancies with PH by examining demographic and clinical characteristics, and the predictors mainly included NT-proBNP, PASP, ALB, RDW, and platelet count (21). Based on these variables, which were screened as predictors by univariable analysis, we first established a well-performing prediction model (the GBDT model) for maternal death. According to the feature importance in the GBDT model, we found that the three most important covariates were NT-proBNP, PASP, and ALB.

In our study, the maternal mortality within 10 days after delivery was 9.4% for all PH patients and 11.7% for PAH patients. The overall outcome was better than that reported 10 years ago (mortality 30–56%) (21). Recent studies by Karen and Marie-Louise reported 10-day mortality rates for PH (3.3–12.2%) and PAH (5.1–16.7%) that were similar to those in our study (8, 9). The reduction in maternal mortality in recent reports reflected advanced medical monitoring during the perinatal period. Consistent with other studies, the most common causes of death were right ventricular failure and shock, occurring at the early stage after delivery (8, 9, 11).

Machine learning in medicine has become a hot topic and is widely used to estimate risk, determine predictors and develop prediction models for diagnosis and prognosis with superior predictive ability (22). Machine learning has been used in the analysis of big data, but the four algorithms employed in this present study, namely, RF, NB, GBDT, and SVM, can also perform well with small sample sizes (23–25). For example, Galatzer-Levy et al. developed post-traumatic stress disorder predictive models by SVM with 152 samples (26); Lee Jollans reported that RF had good performance with a sample size over 200 and could perform across all sample sizes (23). Compared to traditional biostatistics, Machine learning can build models using datasets with more features exceeding the sample size (23).

In our prediction model, NT-proBNP was the most important predictor for maternal death. NT-proBNP, a natriuretic peptide, is released from cardiomyocytes due to ventricular stretch, and an elevated level in PH predicts overload of pressure and heart failure (15). NT-proBNP is also a serum biomarker that has strong predictive value for mortality in adult congenital heart disease (27, 28) and is recommended for risk assessment in PH patients by international guidelines (1). Pregnancy is accompanied by complex hemodynamic changes, including an increase in intravascular volume and cardiac output and a decrease in systemic vascular resistance, affecting the level of natriuretic peptides (29). However, clinical data also revealed that measurement of NT-proBNP had clinical utility in the risk assessment for pregnant women with cardiovascular disease (29,

30). Our study also found that the levels of NT-proBNP had utility in risk assessment and could predict death with a cut-off value of 1519.3 pg/ml and also had a good relative sensitivity and specificity for predicting death during delivery and within 10 days after delivery.

According to the model's feature importance, PASP is another important predictor for high-risk patients and had relatively high sensitivity and specificity in further ROC analysis. The mean PAP and PASP values are not recommended as predictors of risk assessment in the guidelines, mainly because they will decrease with the reduction in stroke volume in the disease's final stage (31). However, in the early or middle phase of the disease, stroke volume shows very little change. Furthermore, pulmonary artery pressure is central to evaluating disease progression and right ventricular dysfunction. An elevated PASP can indicate a high risk for ventricular dysfunction and progression of the disease in the early and middle stages (31, 32). Therefore, there may be two reasons to explain why PASP is a predictor of pregnancy risk in women with PH. First, stroke volume increases during pregnancy, unlike the decline in the final stage of PH (29). Second, the large proportion of women in our study who were asymptomatic and newly diagnosed with PH with WHO functional class I or II were in the early stage of the disease. In one Indian study and another East China study, univariable analysis revealed that maternal mortality increased in women with PASP $>$ 70 mmHg and PASP $>$ 50 mmHg, consistent with our study (5, 33).

In our study, serum albumin was also an important predictor for maternal death, and non-survivors had lower serum albumin, which is related to albumin's biological functions. Albumin plays a vital role in numerous physiological processes, including antithrombotic functions, vascular endothelial stabilization, antioxidants, colloid osmotic pressure maintenance, and microvascular integrity (34). These pathophysiologic processes are relevant for disease progression in patients with PH, and therefore, hypoalbuminemia may represent a non-specific risk marker of more advanced PH (16). Several studies have demonstrated that hypoalbuminemia is linked to reduced survival in the setting of PH or heart failure, which was consistent with our findings (16, 34).

Although the top three most critical features had no highly correlated features (all $r < 0.5$), there was a weak correlation between the Eisenmenger syndrome and PASP ($r = 0.49$). Women with Eisenmenger syndrome also had a higher maternal mortality rate in the present study. Therefore, we should also be aware that the low rank of Eisenmenger syndrome could be affected by the correlation. In addition, Eisenmenger syndrome, a binary variable, has the lower chance for high feature importance than continuous variables in the GBDT model. Therefore, we recommend that patients with Eisenmenger syndrome follow the current guidelines against pregnancy (35).

Limitations

Our study has some limitations. According to the 2015 ESC/ERS guidelines, RHC is the gold standard for diagnosing PH, although Group 2 and 3 patients are not recommended to undergo RHC unless organ transplantation is considered (1). However, RHC is an invasive tool that was not recommended for routine monitoring during pregnancy by a previous study (8) or the Pulmonary Vascular Research Institute guidelines (4). Therefore, we employed both RHC and echocardiogram parameters as diagnostic criteria that were also employed in other studies (5, 8–10). Moreover, a meta-analysis revealed that echocardiography has high sensitivity and specificity (83 and 72%, respectively) for diagnosing PH (36). In addition, we excluded patients with right ventricular outflow tract obstruction/pulmonary stenosis to avoid the negative impact on the estimation of PASP and diagnosis of PH. Furthermore, it remains unclear whether the echocardiogram parameters for diagnosing PH will change with extensive physiological changing during pregnancy. Forty-one (13.7%) patients were diagnosed with PH by echocardiography before delivery; when RHC was performed after delivery, they were all reconfirmed as having PH in our study. The echocardiographic diagnosis is not the gold standard. Therefore, we consider echocardiography as a diagnostic method to be a limitation of our study.

CONCLUSION

Maternal mortality remains high among women with PH, especially those with PAH. Our study demonstrates that NT-proBNP, PASP, and serum albumin levels are significant predictors of death among pregnant women with PH. These findings may help clinicians provide better advice on family planning for women of childbearing age with PH and provide timely and appropriate medical interventions.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Institutional Review Board of The First Affiliated Hospital of Zhengzhou University. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

ZC was the guarantor of submission and participated in the literature search and study design. L-LD, T-CJ, and P-FL participated in the study design, data collection, data analysis, and writing. XW, HS, and YW participated in the study design and figures. L-QJ, ML, and LA participated in data

collection and data verification. X-GJ participated in data collection and data analysis. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.814557/full#supplementary-material

Supplementary Figure 1 | Correlation between variables. BUN, blood urea nitrogen; WHO; APTT, activated partial thromboplastin time; PT, prothrombin time; NT-proBNP, N-terminal brain natriuretic peptide; RDW, Red cell distribution width; PASP, pulmonary artery systolic pressure; RA, right atrium; World Health Organization; PH, pulmonary hypertension.

Supplementary Table 1 | Echocardiographic signs suggesting pulmonary hypertension used to assess the probability of pulmonary hypertension in addition to tricuspid regurgitation velocity measurement.

Supplementary Table 2 | Feature importance across 5-fold cross-validation.

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CASE REPORT
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Case Report: Severe Peripartum Cardiac Disease in Myotonic Dystrophy Type 1

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Background: Myotonic dystrophy type 1 (DM1) is a hereditary muscular dystrophy affecting ∼2.1–14.3/100,000 adults. Cardiac manifestations of DM1 include conduction disorders and rarely cardiomyopathies. DM1 increases the risk of obstetric complications, however, little is known about the relationship between pregnancy and cardiomyopathy in DM1 due to disease rarity.

Case: A 23-year-old with DM1 developed cardiomyopathy during pregnancy. Despite initial medical stabilization, she subsequently developed multiple spontaneous coronary artery dissections postpartum, worsening cardiomyopathy and multiorgan failure. She died 5 months postpartum.

Conclusion: Though cardiomyopathy and arterial dissection are both known complications of pregnancy, this case suggests individuals with myotonic dystrophy type 1 may be at heightened risk for cardiac disease during the peripartum period. Physicians caring for women with suspected or proven DM1 should offer counseling and be alerted to the risk of cardiac complications with pregnancy and in the peripartum period. Pregnant and peripartum women with DM1 are likely to benefit from more frequent assessments of cardiac function including echocardiograms and early institution of heart failure management protocols when symptoms of cardiomyopathy present.

Keywords: pregnancy, cardiomyopathy, spontaneous coronary artery dissection, neuromuscular disease, cardiovascular

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INTRODUCTION

Myotonic dystrophy type 1 (DM1) is one of the most common inherited muscular dystrophies in adults, with a worldwide prevalence of 2.1–14.3/100,000 (1). It is an autosomal dominant disorder, caused by the expansion of a trinucleotide (CTG) repeat sequence in the 3′ untranslated region of the myotonic dystrophy protein kinase gene (*DMPK*), located on chromosome 19q13.32 (2, 3). DM1 can present at any age and the clinical phenotype ranges from asymptomatic to severe congenital disease. Classic DM1 presents with facial and distal muscle weakness, myotonia, and cataracts in adults. DM1 patients may also have serious systemic manifestations, including central

nervous system involvement, cardiac arrhythmias, and gastrointestinal disorders (4). Currently, there are no approved genetic therapies for DM1.

Cardiac involvement in DM1 is known to increase the risk of sudden cardiac death (5). Cardiac abnormalities in DM1 include conduction defects (atrioventricular block, bundle branch blocks, and intraventricular block), arrhythmias (supraventricular or ventricular tachyarrhythmias) and less commonly, cardiomyopathy and valvular disease (5–7). The most prevalent cardiac defects are conduction abnormalities, which occur in approximately 65% of patients (4). Cardiac muscle myotonia or fibrosis may contribute to left ventricular diastolic dysfunction (8). The prevalence of left ventricular systolic dysfunction in DM1 patients ranges between 7.2 and 18.9% (5, 9, 10), however most DM1 patients do not exhibit symptoms of heart failure. Both left ventricular systolic dysfunction and heart failure are significantly associated with all-cause death and cardiac death (9).

Women with DM1 are at risk of complications during pregnancy, including increased need for caesarian section (31–36.7%), pre-term labor (30–35.0%), polyhydramnios (10–25%), miscarriage (12–15.3%), urinary tract infection (9.4%), pre-eclampsia (9–9.5%), placenta previa (4–10.8%), and ectopic pregnancy (3.5–4%) (11–13). The frequency of perinatal mortality ranges from 10 to 23%, compared to 0.5–1% in the general population (11). Select symptoms of DM1, including myotonia, mobility limitations, fatigue and pain may progress during pregnancy and in some cases may not return to baseline until 6 months after pregnancy (13). In addition, many women are unaware that they are affected with DM1 before they become pregnant and may be diagnosed after their affected child displays DM1 symptoms (11).

One previous case report described a patient with DM1 who developed cardiomyopathy and died of a cardiac arrest 8 weeks postpartum (14). The second comparable observation we report here, with the additional novel finding of multiple spontaneous coronary arterial dissections, increases the likelihood of a true etiological link between DM1 and cardiac complications of pregnancy.

CASE

A 23-year-old woman was referred to the Neuromuscular Clinic at The Ottawa Hospital for assessment of muscle stiffness. A diagnosis of DM1 was made based on the presence of classical clinical features (grip myotonia, ptosis, distal hand, leg, face, and neck weakness, hypotonia and hypersomnolence). Genetic testing revealed 750–850 CTG repeats in *DMPK*, consistent with DM1. There was no known family history of DM1 at the time of diagnosis, however, her father and sister were subsequently determined to be affected clinically and confirmed with molecular diagnosis. There was no history of cardiomyopathy, coronary artery disease, valvular heart disease or arrhythmia. Initial cardiac screening with transthoracic echocardiogram and electrocardiogram were normal. She did not present with obesity, did not smoke, and had no history of diabetes, or dyslipidemia. There is no disease-modifying treatment available for DM1. A timeline is shown in **Figure 1**.

The proband subsequently became pregnant at age 23. She developed mild dyspnea in the 7th month of pregnancy. Repeat transthoracic echocardiogram at 38 weeks gestation demonstrated an ejection fraction of 35–40% [normal > 55% (15)]. She was admitted to the high-risk obstetrical unit at 39 weeks gestation due a non-reassuring fetal heart rate and worsening dyspnea. She had a spontaneous vaginal delivery at 39 + 3 weeks, complicated by postpartum hemorrhage requiring transfusion. Her child was healthy. She was diagnosed with peripartum cardiomyopathy but was otherwise feeling well and discharged home with metoprolol to be followed by cardiology as an outpatient.

Five days postpartum, she developed acute retrosternal chest pain radiating to the jaw and left arm. In the emergency room, electrocardiogram demonstrated inferior lead ST elevation and she was immediately taken to the cardiac catheterization lab. Cardiac catheterization demonstrated multivessel spontaneous coronary artery dissection (SCAD) involving the ostial left main artery, first diagonal artery, obtuse marginal branches (M2 and M3 branches) and distal left anterior descending coronary artery (**Figure 2**). The patient had a cardiac arrest during the procedure, requiring cardiac resuscitation, intubation, and vasopressors for hemodynamic support. She stabilized rapidly and was able to be extubated within 24 h. She was started on guideline directed medical therapy for heart failure including angiotensin converting enzyme inhibitor, beta-blocker, and mineralocorticoid receptor antagonist and aspirin for SCAD. Repeat echocardiogram demonstrated a left ventricular ejection fraction of 20% with left ventricular dilatation, and mild mitral and tricuspid regurgitation. Cardiac magnetic resonance imaging confirmed left ventricular dilatation with severe left ventricular dysfunction, thin linear mid-wall delayed gadolinium enhancement in the septum, and focal transmural late gadolinium enhancement at the mid to base left ventricular inferior and inferolateral walls with hypokinesia secondary to SCAD (**Figure 2**). Ultrasound demonstrated left internal jugular vascular line associated thrombus and she was treated with apixaban for 3 months. She improved rapidly, was ambulant and discharged home 12 days later and remained clinically stable for 5 months.

After several months, the patient discontinued her medications (aspirin, spironolactone, and perindopril), as she was concerned that these medications were causing abdominal pain. She acutely declined and she was readmitted to hospital with nausea, abdominal pain, orthopnea, and paroxysmal nocturnal dyspnea with a diagnosis of heart failure. Transthoracic echocardiogram demonstrated worsening cardiac function with severe global hypokinesis of the left ventricle, mild to moderately reduced right ventricular systolic function, severe functional mitral regurgitation, moderate tricuspid regurgitation and pericardial effusion (**Figure 3**). Given persistent severe low left ventricular ejection fraction, a dual chamber implantable cardioverter defibrillator was implanted for primary prevention. However, she deteriorated rapidly, developed further cardiogenic shock, and had multiple cardiac arrests with pulseless electrical

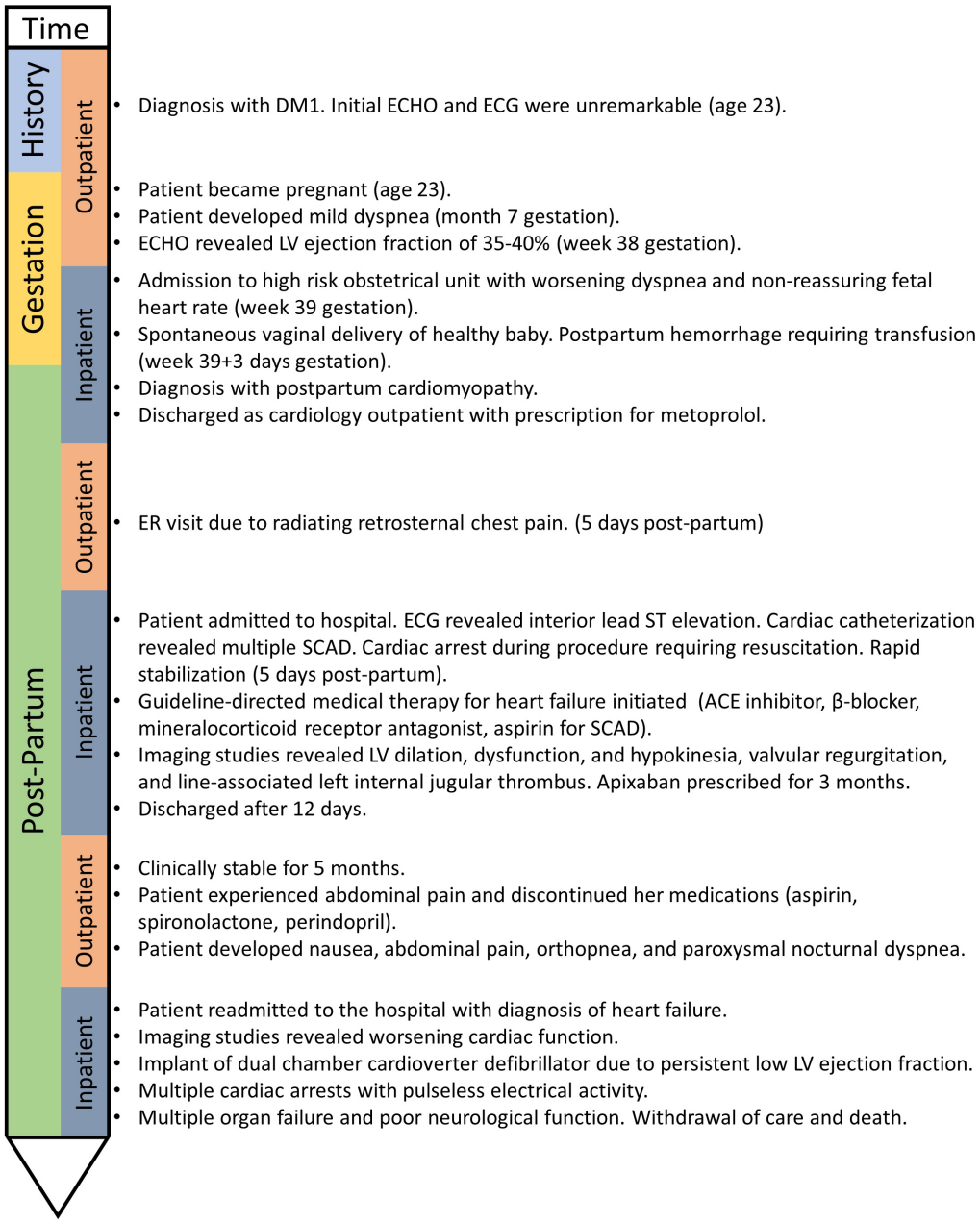

FIGURE 1 | Case timeline.

activity. She required extracorporeal membrane oxygenation, cardiac support with a miniaturized ventricular assist pump/left ventricular assistive Impella device with anticoagulation, and renal replacement therapy. She had several complications including renal failure and septicemia and developed pneumonia with computerized tomography chest demonstrating confluent consolidation in the upper and lower lung lobes. Computerized tomography abdomen showed severe congestive hepatopathy and bowel ischemia. Unfortunately, she also developed multiple large epidural and subdural hematomas and cerebral edema with worsening neurological function. Care was withdrawn due to poor neurological and cardiac function with multiorgan failure. No autopsy was performed.

DISCUSSION

Cardiac involvement is prevalent in DM1, occurring in approximately 80% of patients (16). Although arrhythmias and conduction defects are more common in DM1 patients, dilated cardiomyopathy has been reported (16). Larger CTG repeat expansions have been associated with a greater risk of left

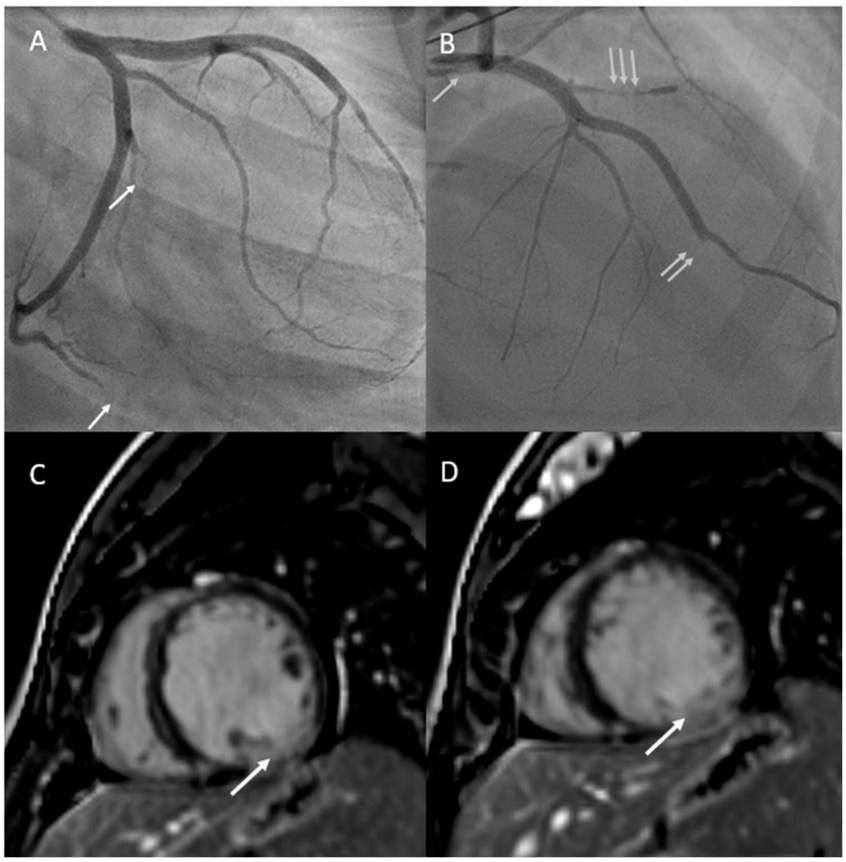

FIGURE 2 | (A) Depicts cardiac angiogram demonstrating occluded cardiac marginal arteries (arrows). **(B)** Depicts cardiac angiogram demonstrating dissected left main coronary artery (single arrow), occluded left anterior descending artery (double arrow), and occluded diagonal artery from the left anterior descending artery (triple arrow). **(C,D)** Reveal cardiac MRI with gadolinium enhancement with phase sensitive inversion recovery showing basal to mid transmural late gadolinium enhancement in the inferior and inferolateral walls (left circumflex artery territory) secondary to spontaneous coronary artery dissection.

ventricular dysfunction, conduction defects, supraventricular arrhythmias, and sudden death (17). Women with DM1 are at an increased risk of pregnancy complications, including death (11).

Peripartum cardiomyopathy is defined as heart failure secondary to left ventricular systolic dysfunction (left ventricular ejection fraction $< 45\%$, 45–50% on occasion (18)) without an identifiable etiology that occurs in the last month of pregnancy or within 5 months post-delivery (19). The incidence of peripartum cardiomyopathy widely varies geographically and is estimated to be between 1/900 and 1/4,000 live births in the United States (20). Complications of peripartum cardiomyopathy include thromboembolism, cardiogenic shock, arrhythmias, cardiac arrest, and sudden death (20). If treatment for peripartum cardiomyopathy is started rapidly, patients may have a partial or full recovery of cardiac function but remain at increased risk of relapse, particular with subsequent pregnancies (21). Peripartum cardiomyopathy management includes standard heart failure treatment and bromocriptine (a prolactin inhibitor) with thrombosis prophylaxis or anticoagulation (21). Bromocriptine was not given for this patient due to internal jugular thrombosis. Standard heart failure treatment, including angiotensin-converting enzyme inhibitors and beta-blockers, is strongly recommended for the treatment of dilated cardiomyopathy in neuromuscular diseases (4). A pacemaker is indicated in case of bradycardia or atrioventricular blocks, whereas symptomatic ventricular arrhythmias may require an implantable cardioverter defibrillator (4). Cardiac transplantation may be considered in motivated, ambulant patients with advanced heart failure and relatively good neuromuscular prognosis (4). Unfortunately, the patient presented in this report had developed severe multiorgan dysfunction and was not a candidate for transplant.

SCAD is a non-iatrogenic, non-traumatic and non-atherosclerotic intramural hemorrhage, causing separation of the coronary arterial wall (22). This intimal tear or spontaneous hemorrhage results in a false lumen with intramural hematoma that can compress the true lumen, causing myocardial ischemia or infarction (23). SCAD accounts for up to 35% of myocardial infarctions in women under 50 years of age and can cause cardiac arrest, myocardial infarction, or death (23).

SCAD has been associated with postpartum status, multiparity, arteriopathies, connective tissue disorders, systemic inflammatory conditions, emotional distress, and up to 86% of patients have fibromuscular dysplasia (24, 25). Pregnancy-associated SCAD can occur in the antepartum or postpartum

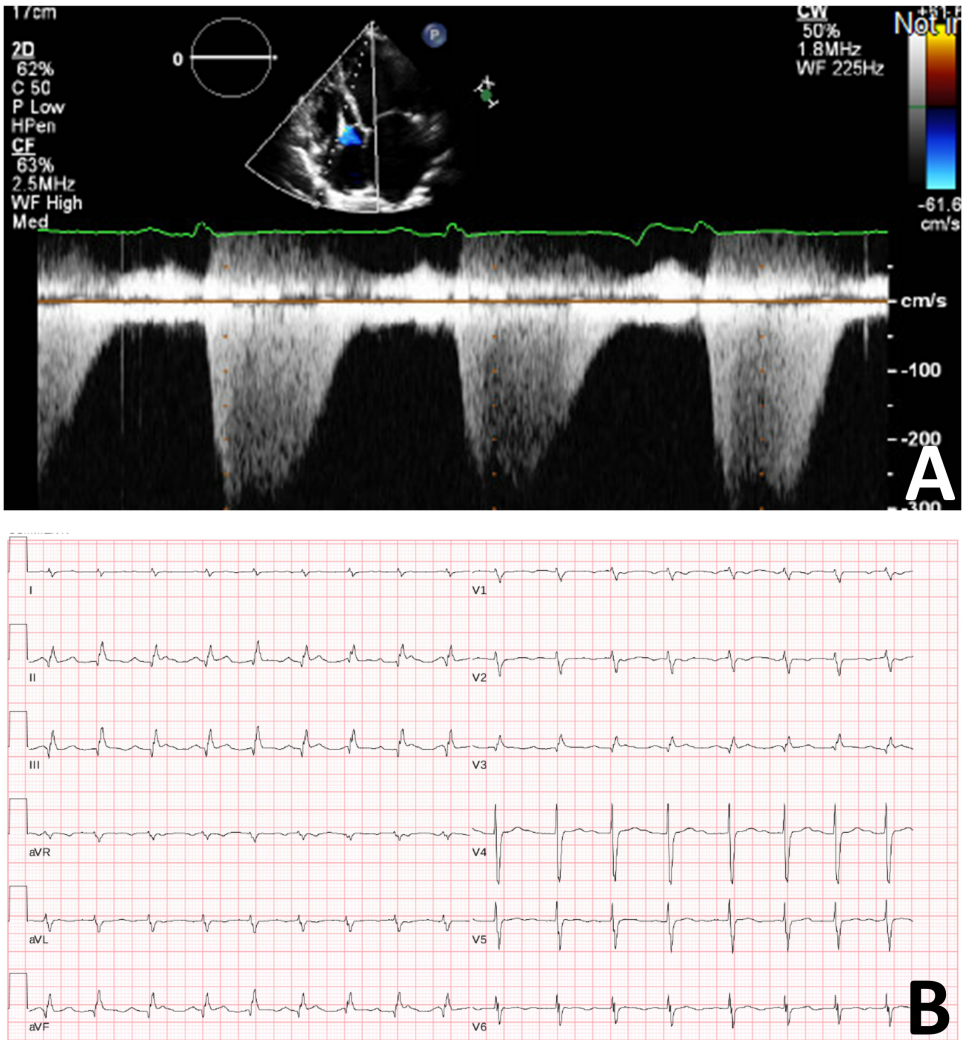

FIGURE 3 | (A) Transthoracic cardiogram demonstrating severely reduced LV function with severe biatrial enlargement. **(B)** Electrocardiogram demonstrating sinus tachycardia with second degree A-V block (Mobitz 1).

period and is believed to be caused by the hormonal and hemodynamic changes of pregnancy (22). While early research suggested that SCAD is commonly associated with pregnancy, more recent studies have shown that pregnancy-associated SCAD represents < 5% of SCAD cases (18). Apart from being postpartum, our patient was not found to have any underlying conditions known to be associated with SCAD. Vascular imaging did not demonstrate fibromuscular dysplasia and she did not have clinical evidence of a connective tissue disorder or systemic inflammatory condition. Her underlying diagnosis of DM1 raises the possibility of an association with SCAD. While there have been no previous reports of SCAD in peripartum DM1 patients, DM1 is associated with vascular dysfunction, including systemic reductions in blood pressure (26, 27), increased susceptibility to orthostatic hypotension (28), lower coronary reserve (29), and thinner capillary basement membranes (30). It is conceivable that DM1-related vascular dysfunction, pregnancy-induced changes in cardiovascular function, and the exertional stresses of labor and delivery could place DM1 patients at elevated risk of SCAD in the peripartum period.

This is the first reported case of SCAD, and the second reported case of fatal peripartum cardiomyopathy in a DM1 patient. As the etiology of SCAD is thought to be multifactorial, there may have been several precipitating factors in this case, including postpartum hormonal status and cardiomyopathy. In most cases, conservative management of SCAD is preferred as the coronary artery intimal tear has been shown to heal spontaneously (23). Medical management of SCAD includes antiplatelets and beta-blockers. Revascularization is usually reserved for patients with ongoing ischemia or hemodynamic instability (23).

The previous report by Fall et al. (14) described one patient with DM1 who developed severe diuretic-resistant

cardiomyopathy (ejection fraction 20%) and underwent dialysis for treatment of pulmonary edema prior to cesarian delivery. The patient clinically improved over 2 months with resolution of dyspnea and peripheral edema. However, she died suddenly 8 weeks postpartum from cardiac arrest (14). The combined rarity of DM1, SCAD, and severe peripartum cardiomyopathy coupled with the absence of DM1-specific treatments for heart failure were diagnostic and therapeutic challenges in the present case. This report serves to alert clinicians to the potential risk of severe cardiac disease and SCAD in DM1 patients. It also offers a strategy to increase our understanding of, and potentially mitigate, risks to DM1 patients in the future.

Physicians caring for women with suspected or proven DM1 should offer counseling and be alerted to the risk of cardiac complications with pregnancy. In addition to routine baseline cardiac function studies, any symptomatology suggestive of heart failure should prompt further dedicated cardiologic assessment. At present, there are no DM1-specific treatments. Patients who develop a cardiomyopathy are likely to benefit from early institution of standard heart failure management to prevent deterioration in cardiac function and reduce the risk of heart failure. Further research and ongoing enrollment in DM1 patient registries are required to better define the incidence of peripartum cardiomyopathy and SCAD, as well as the best therapeutic strategy for this unique clinical challenge to the growing field of cardio-obstetrics.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article. Further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The legal representatives of the patient have provided written informed consent in support of this publication and for any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

GB and JW-C curated the patient data and drafted the initial manuscript. All authors reviewed the literature and edited the manuscript for scientific content.

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Impact of Educational Interventions on Knowledge About Hypertensive Disorders of Pregnancy Among Pregnant Women: A Systematic Review

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Background: Hypertensive disorders of pregnancy (HDP), including chronic hypertension, preeclampsia and gestational hypertension, is the cause of about 50,000 deaths out of 400,000 perinatal deaths. HDP is an effective risk factor in stroke, type 2 diabetes, and cardiovascular diseases like ischemic heart disease. There is a significant relation between HDP, lifestyle, and knowledge. Unfortunately, many studies showed that pregnant women have lack of knowledge about HDP. Therefore, the importance of educational interventions is, today, more acknowledged than before.

Aim: The goal of this systematic review was to investigate the effect of interventional educations on the knowledge of pregnant women about HDP.

Methods: A systematic review of the related articles was conducted. We included English randomized controlled trials published up to December 2021, including pregnant women as population, HDP as the outcome, and educational interventions as the intervention.

Results: After the process of study selection, six articles containing 819 pregnant women were included in this study. Educational pamphlets, mobile-based application, a mixture of pamphlets, pictographic magnet and videos, and a combination of PowerPoint and data show projectors and conversation were the educational interventions in these studies.

Conclusions: The positive effects of educational interventions on the knowledge of women with HTP were observed in all studies. The higher knowledge leads to HDP-related complications.

Systematic Review Registration: https://archive.org/details/osf-registrations-gcs5r-v1, identifier: doi: 10.17605/OSF.IO/GCS5R.

Keywords: hypertensive disorders of pregnancy, preeclampsia, education, hypertension, pregnancy

INTRODUCTION

Hypertensive disorders of pregnancy (HDP) is observed in 5–10% of pregnant women worldwide (1). Chronic hypertension, preeclampsia, and gestational hypertension are the three types of HDP. Chronic hypertension, as a hypertension diagnosed before pregnancy or before the 20th week of pregnancy, may convert to preeclampsia. Gestational hypertension, occurred after 20 weeks of pregnancy, can also lead to preeclampsia (2). Preeclampsia is a hypertensive disorder characterized by proteinuria and the onset of hypertension beginning after 20 weeks of pregnancy (3). More than 50,000 deaths of mothers and 400,000 of perinatal deaths happen because of HDP, specially preeclampsia, each year (4, 5). The incidence of stroke and ischemic heart disease in women with preeclampsia is about 2.5 times higher than normal pregnancies (6, 7). The risks of renal disease and type 2 diabetes are also elevated by preeclampsia (8). In addition to preeclampsia, gestational hypertension and chronic hypertension are also long-term risk factors in cardiovascular disease (9). Nowadays, some screening programs are performed all over the world for the identification of women with the signs of preeclampsia. Cooperation of the women is one of the most important factors in the success of these programs. The cooperation is associated with the knowledge and the level of education of pregnant women (10, 11). Many studies found out that pregnant women had poor knowledge about increased cardiovascular risks after HDP (12). Pregnant women often do not participate in the programs for life-style changing because of low amount of knowledge, lack of suitable follow-up, and, also, the higher price of healthier food (13–15). Studies indicated that poor education levels of pregnant women led to dangerous conditions like pre-mature delivery or death of neonates (16). Researchers indicated that women were assessed for their cardiovascular disease less than men or the assessment was generally performed after the diagnosis among them (17). This makes the importance of knowledge of pregnant women about HDP more than before. The patient's knowledge plays an important role in preventing risk factors like cardiovascular disease, monitoring blood pressure, and helping the patient to know about the condition of severity of the disease, symptoms, and the management of them by a good lifestyle, including appropriate diet and lifestyle modifications (18). As noted, due to the importance of increasing the levels of education among pregnant women about HDP, different educational interventions were used in studies. Mobile-based applications, graphics-based educational tools, and pictorial cards are some of the examples (19–21). As far as we know, there are no presently available systematic reviews on the impact of educational interventions on knowledge of pregnant women about HDP. This review can help the medical staff and pregnant women for better choice of educational interventions to better manage HDP.

METHODS

This systematic review study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA2020) Statement (22). In accordance with the PICO criteria, the "participants" were exclusive to pregnant women; the types of "intervention" covered were educational interventions; the "comparator" was not determined; and the "outcome" was knowledge about HDP. This review has been registered on The Open Science Framework (OSF) (Registration doi: 10.17605/OSF.IO/GCS5R available at https://archive.org/details/osf-registrations-gcs5r-v1).

Search Strategy

We identified original RCTs through searching for English language articles published up to December 2021 in PubMed/MEDLINE, Scopus, Google Scholar, and Cochrane Central Register of Controlled Trials (CENTRAL) databases. Additionally, the duplicate records were removed using EndNote (v.7, Thomson Reuters, Toronto, Canada). Two reviewers (MD and KGh) developed the search strategy as followed: ("hypertension*" OR "hypertensive" OR "hypertensive disorders") AND ("education*" OR "inform*" OR "knowledge") AND ("pregnancy" OR "pregnant"). **Table 1** shows the search strategies for PubMed/Medline, Scopus, and central databases. We also screened the references of relevant studies to identify eligible studies. The PRISMA flow diagram is available in **Figure 1**.

Inclusion Criteria

All primary research studies that found the following PICOS criteria were included for review if:

(A) Population: pregnant women (P);
(B) Interventions: educational intervention (I);
(C) The control group: standard care or forfeiture of any intervention; if there was no control group (C);
(D) Type of the primary outcome: hypertensive disorders of pregnancy (O);
(E) Type of study design: English language RCTs (S).

Data Screening and Extraction

Two reviewers (ShK and AJA) assessed and screened titles and abstracts to recognize related studies using a form developed by the research team. Full texts of studies were retrieved for "Yes" and "Maybe" assessment for eligibility study. We

TABLE 1 | Search strategies for PubMed, Scopus, and central databases.

Search engine	Search strategy	Additional filters
PubMed/MEDLINE	(education[tiab] OR educate[tiab] OR educational[tiab] OR inform [tiab] OR informative[tiab] OR "education" [Mesh] OR "educate"[Mesh] OR "educational" [Mesh] OR "inform" [Mesh] OR "informative"[Mesh]) AND (hypertension[tiab] OR hypertensive[tiab] OR "hypertension" [Mesh] OR "hypertensive"[Mesh]) AND (knowledge[tiab] OR "knowledge"[Mesh]) AND (pregnant [tiab] OR pregnancy[tiab] OR preeclampsia[tiab] OR Hypertension, Pregnancy-Induced[tiab] OR "pregnant"[Mesh] OR "pregnancy" [Mesh] OR "preeclampsia"[Mesh] OR "Hypertension, Pregnancy-Induced"[Mesh]) AND (intervention[tiab] OR "intervention" [Mesh])	**English, December 1st, 2021**
Scopus	(education* OR educate* OR educational* OR inform* OR informative*) AND (hypertension* OR hypertensive*) AND (knowledge*) AND (pregnant* OR pregnancy* OR preeclampsia* OR Hypertension, Pregnancy-Induced*) AND (Intervention*)	**English, December 2nd, 2021**
Central	#1: (Educate):ti,ab,kw OR (Educational):ti,ab,kw OR (Education):ti,ab,kw OR (inform*):ti,ab,kw OR (Knowledge):ti,ab,kw #2: MeSH descriptor: [Education] explode all trees #3: (Pregnant):ti,ab,kw OR (Pregnancy):ti,ab,kw OR (preeclampsia):ti,ab,kw #4: MeSH descriptor: [Pregnancy] this term only #5: (Hypertension):ti,ab,kw OR (Hypertensive):ti,ab,kw #6: MeSH descriptor: [Hypertension] explode all trees #7: #1 OR #2 #8: #3 OR #4 #9: #5 OR #6 #10: #7 AND #8 AND #9	**English, December 21st, 2021**

resolved discrepancies and disagreement by consensus. Data extraction was completed by two independent assessors (MS and HGh). Discrepancies were resolved by consensus and discussion between two reviewers.

Quality Assessment of Included Studies

For each study, two assessors (YS and KGh) independently assessed all included studies according to the Cochrane risk of bias tool (23). The Cochrane risk of bias tool is a standard and common tool that includes all the essential questions to determine and judge the methodological quality and the risk of bias focusing on 6 domains, including sequence generation, allocation concealment, blinding, in-complete data, and selective reporting, and other bias and disagreement were resolved by consensus and discussion *via* two assessors (**Figure 2**).

RESULTS

Through the process of selection, six articles were included in this study; the summary of the findings of included studies is summarized in **Table 2**. All of the included studies were randomized clinical trials. Three of the studies were performed in Canada. The other studies were conducted in Iran, Jordan, and China. These studies investigated the effect of educational interventions on some obstetrics and non-obstetrics outcomes, such as knowledge, Apgar score, systolic blood pressure (SBP), diastolic blood pressure (DBP), satisfaction, awareness, weight gain, and anxiety about hypertensive disorders of pregnancy (including pre-eclampsia and gestational hypertensive disease) among 910 pregnant women. The most frequent disorder was pre-eclampsia. Various educational intervention tools were used for assessment of efficacy of education in the included studies: educational pamphlets (27, 28), mobile-based educational application (11), a combination of pamphlets, pictographic magnet, and videos (24), prenatal health education and nutrition interventions (29), and a mixture of PowerPoint, as well as data, show projectors and conversation (26) were used for the purpose of education (**Table 2**). All studies reported a positive impact of educational interventions on the hypertensive disorders of pregnancy. Not only the educational interventions improved the obstetrics outcomes, but also the non-obstetric parameters were affected by them. Overall, the significant higher knowledge score (24, 26), greater levels of decreased DBP (26, 28), reduced SBP (28), the higher Apgar score (26) and satisfaction (26, 28), and more awareness about HDP complications (26) were observed in the included studies (The p-value of the mentioned outcomes was reported <0.05 in the articles).

DISCUSSION

The present study reviewed research on the effect of educational intervention on pregnant women's knowledge about HDP (including chronic hypertension, preeclampsia, and gestational hypertension). All included studies showed that providing training related to HDP is effective in increasing pregnant women's knowledge about the disease. Accordingly, providing educational interventions through various methods, including mobile applications (11), pamphlets (24, 27, 28), face-to-face training approaches (25, 26), and a combination of different training methods, increases the knowledge of pregnant women in this regard.

The low mean score of pre-eclampsia knowledge before the educational intervention indicates a very poor perception of possible risks of elevated hypertension by pregnant mothers (11). So, increasing relevant knowledge results in

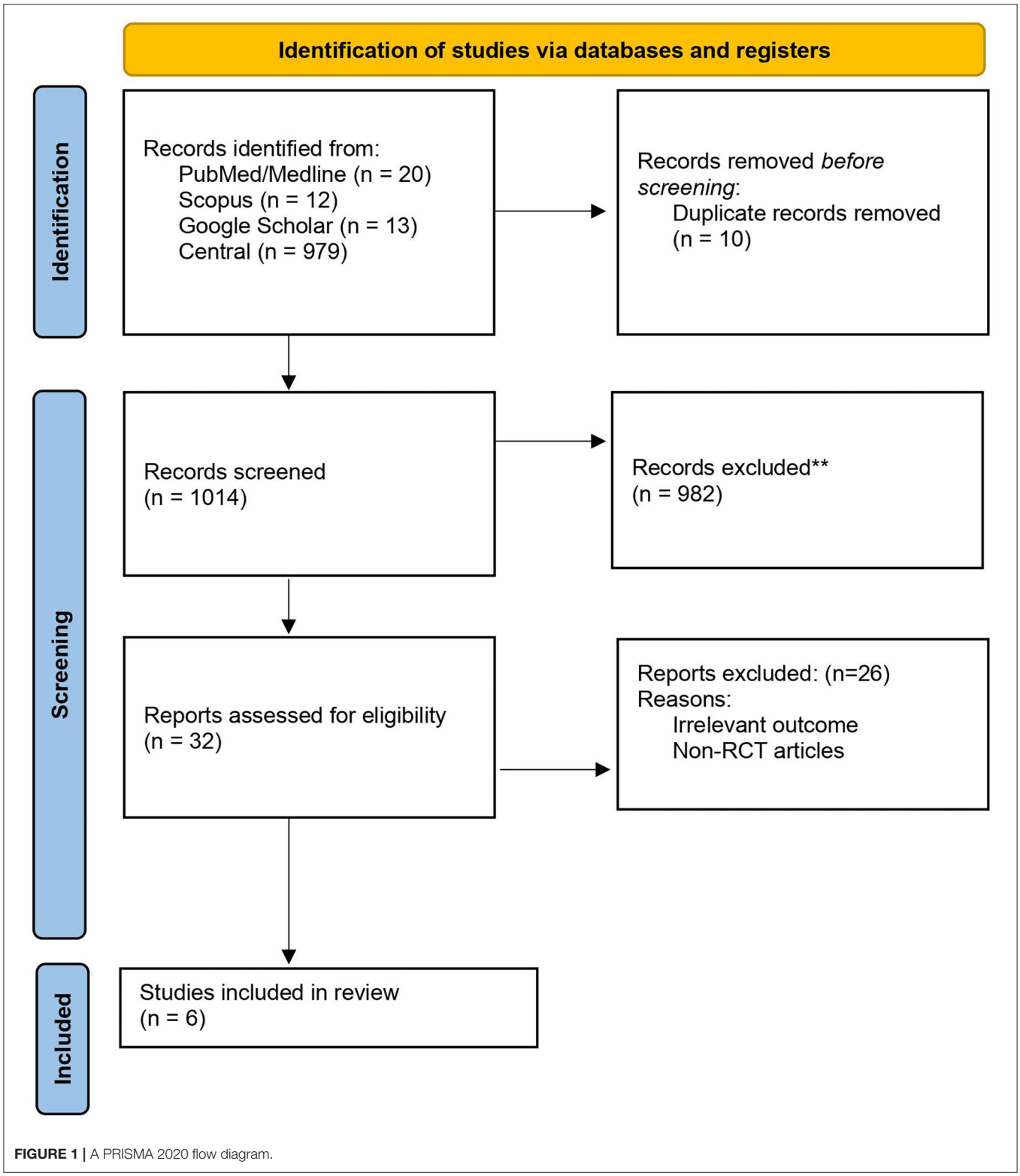

FIGURE 1 | A PRISMA 2020 flow diagram.

early awareness about the signs and symptoms leading to timely referral to physicians which, in turn, followed by suitable care and treatment, which totally provide healthier outcomes for both mothers and babies (30). Evenly, this kind of intervention was considered as the fundamental element for the recovery of maternal hypertension, which prepares the healthy conditions for pregnant women (25).

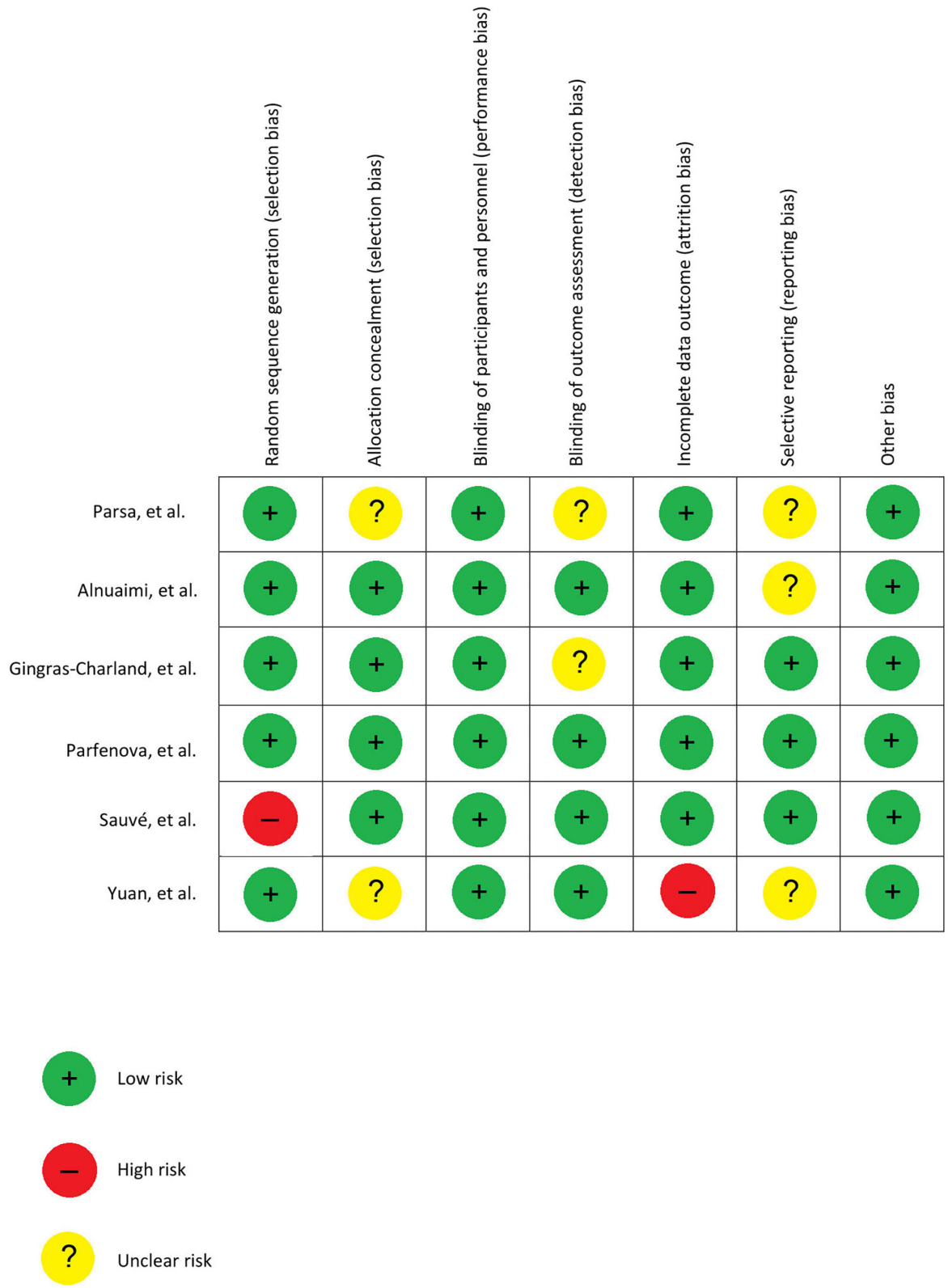

FIGURE 2 | Risk of bias of the included RCTs.

TABLE 2 | A summary of the findings of the included studies.

First author	Year	Country	Type of study	Number of participants	Mean age intervention (±SD)	Hypertensive disorder of pregnancy	Educational intervention type	The time of intervention	Association of educational knowledge intervention on disorders about hypertensive of pregnancy	Obstetrics outcome overall	Obstetrics outcome (intervenrion) (±SD)	Obstetrics outcome (control) (±SD)	*P*-value	Non obstetrics outcome	Obstetrics outcome (intervenrion) (±SD)	Obstetrics outcome (control) (±SD)	*P*-value	Reference
Parsa	2019	Iran	RCT	108	27.93±5.1	Pre-eclampsia	A mobile-based educational application	12 weeks	Yes	Knowledge about the symptoms, signs and complications of preeclampsia increased and adverse effects were reduced.	HDP Knowledge score: Before: 14.84±17.55 After: 78.08 ±14.19	HDPKnowledge score: Before: 14.56±17.55 After: 15.75±19.49	0.94	A mobile-based educational application improved health recovery and managing the condition, enhanced participation in preventive behaviors.	No statistics reported	No statistics reported	No statistics reported	(11)
Gingras-Charland	2018	Canada	RCT	362	28.9±.6	Pre-eclampsia	An informative pamphlet, a video, and a pictographic magnet	4 weeks	Yes	Significant increase in knowledge about risk factors, symptoms, complications for the fetus or newborn and complications for mother and treatments.	HDPKnowledge scores: 70.1±19.2	HDPKnowledge scores: 51.1±23.4	<0.001	Educational intervention raised satisfaction and had no significant effects on the level of anxiety.	Anxiety: 2.40 ± 1.07 Satisfaction : 5.1±0.7	Anxiety: 2.53 ± 0.95 Satisfaction: between 1.7 and 3.8	*P*-values Anxiety: <0.001 satisfaction: 0.007	(24)
Yuan P	2018	China	RCT	90	34.4±4.3	Gestational hypertensive disease	Prenatal health education and nutrition interventions (More emphasis is placed on using interpretative, encouraging, persuasive language to explain relevant knowledge to patients and clarify their necessity.)	Not reported	Yes	Systolic and diastolic blood pressure decreased significantly and adverse consequences were reduced.	Systolic blood pressure: 134±3 Diastolic blood pressure: 83±2	Systolic blood pressure: 148±5 Diastolic blood pressure: 95±1	$P < 0.05$	Prenatal health education and nutrition interventions caused weight gain of pregnant women, raised satisfaction, maintained personal health, improved comfort and prognosis and quality of life.	weight gain: Low level: 3(6.7%) Normal level: 40(88.9%) High level: 2(4.4%) Satisfaction: 93.3%	weight gain: Low level: 10(22.2%) Normal level: 24(53.3%) High level: 11(24.4%) Satisfaction 71.1%	*P*-values (weight and satisfaction) <0.05	(25)

(Continued)

TABLE 2 | Continued

First author	Year	Country	Type of study	Number of participants	Mean age intervention (±SD)	Hypertensive disorder of pregnancy	Educational intervention type	The time of intervention	Association of educational knowledge intervention on disorders about hypertensive of pregnancy	Obstetrics outcome overall	Obstetrics outcome (intervenrion) (±SD)	Obstetrics outcome (control) (±SD)	*P*-value	Non obstetrics outcome	Obstetrics outcome (intervenrion) (±SD)	Obstetrics outcome (control) (±SD)	*P*-value	Reference
K. Alnuaim	2020	Jordan	RCT	113	29.87	Pre- eclampsia	An interventional programabout preeclampsia on high-risk preeclampsia Jordanian women's awareness and pregnancy outcomes (using PowerPoint and a data show projector using interactive images and conversation to educate participants in each group about the selected topics)	12 weeks	Yes	Promote Apgar score/ significant decrease in diastolic blood pressure/ no significant differences in terms of gestational age, newborn weight, systolic blood pressure, mode of birth, NICU admission, mother newborn status (dead or alive) and the final diagnosis/ improve awareness about preeclampsia complication, risk factors, signs and symptoms, prevention, management and preeclampsia definition/ better perfusion and performance of placentas.	Apgar score (1st min): 6.82± 1.42 Apgar score(5th min):8.32±0.95 systolic blood pressure: 116 ±18.8 diastolic blood pressure: 74 ±11.4	Apgar score(1st min): 6.05±1.63 Apgar score(5th min): 7.82 ±1.31 systolic blood pressure: 117 ±19.2 diastolic blood pressure: 79±13.1	*p*-value apgar score(1st min): 0.008 *p*-value apgar(5 st min): 0.024 *p*-value systolic blood pressure : 0.942 *p*-value diastolic blood pressure : 0.019	Total awareness increased significantly in interventional group	Total awareness: Before: 13.228±5.19 After: 27.122 ± 4.157	Total awareness: Before: 11.267 ±9.27 After: 11.5 ± 8.115	*P*-value (total awareness)= 0.00	(26)
Nadine Sauvé, MD	2008	Canada	RCT	100	29.71	Pre- eclampsia	Educational pamphlet	Not reported	Yes	Significant increase in knowledge about risk factors, symptoms, fetal complications, maternal complications and treatment.	Knowledge about fetal complications: 94% Knowledge about Maternal complications of death : 84% Knowledge about delivery treatment : 90% Knowledge about Antihypertensive: 84%	Knowledge about fetal complications: 86% Knowledge about Maternal complications of death 41% Knowledge about delivery treatment : 78% Knowledge about Antihypertensive: 78%	*P*-value fetal complications : 0.19 *p*-value Knowledge about Maternal complications of death : <0.01 *p*-value Knowledge about delivery treatment : 0.09 *p*-value Knowledge about Antihypertensive: 0.39	Educational pamphlet decreased level of anxiety about baby's health, increased level of anxiety about mother's health, raised satisfaction.	Anxiety field of mother's health: 3.90 Anxiety field of baby's physical health: 4.70	Anxiety field of mother's health: 3.73 Anxiety field of baby's physical health: 4.87	*p*-value Mother's health: 0.54 *p*-value Baby's physical health: 0.52	(27)

(Continued)

TABLE 2 | Continued

First author	Year	Country	Type of study	Number of participants	Mean age intervention (±SD)	Hypertensive disorder of pregnancy	Educational intervention type	The time of intervention	Association of educational knowledge intervention about hypertensive disorders of pregnancy	Obstetrics outcome overall	Obstetrics outcome (intervenrion) (±SD)	Obstetrics outcome (control) (±SD)	*P*-value	Non obstetrics outcome	Obstetrics outcome (intervenrion) (±SD)	Obstetrics outcome (control) (±SD)	*P*-value	Reference
Maria Parfenova, MD	2020	Canada	RCT	137	30.9	preeclampsia, eclampsia, gestational hypertension, and pre-existing hypertension	educational pamphlet	68 weeks	Yes	Knowledge about risk for future pregnancy improved and global knowledge score raised.	Global knowledge score (before): 69.4% Global knowledge score (after 1 months) :88.2% Knowledge about future pregnancy (before): 64.6% Knowledge about future pregnancy (after 1 months): 87.6%	Global knowledge score (before): 71.4% Global knowledge score (after 1 months) : 71.3% Knowledge about future pregnancy (before): 65.9% Knowledge about future pregnancy (after 1 months): 67.9%	*P*-value Global knowledge< 0.0001	Educational pamphlet improved knowledge about risk for future health, increased risk perception of heart disease, but no difference for hypertension or stroke, raised satisfaction and had no effect on the level of anxiety.	Knowledge about risk perception of heart disease (before) : 4.0 ± 0.78 Knowledge about risk perception of heart disease (after): 4.3 ± 0.94 satisfaction: 5.6 ± 0.66 Anxiety (before): 3.7 ± 1.0 Anxiety (after): 3.8 ± 1.0	Knowledge about risk perception of heart disease (before) 3.9 ±1.14 Knowledge about risk perception of heart disease (after): 4.0 ± 0.97 satisfaction: 3.6 ± 1.33 Anxiety (before): 3.9 ± 1.1 Anxiety (after): 4.0 ± 1.0	*p*-value increased risk perception of heart disease: 0.036 *p*-value satisfiction < 0.0001 *p*-value anxiety : 0.6746	(28)

A graphitic educational tool increased the knowledge of pre-eclampsia 8 and 22% compared with standard pamphlets and peers with no education, respectively (21). However, the impact of a mobile-based educational application on the knowledge of the subjects was considerably higher (11). This increased growth in the level of knowledge that is related to the type of educational intervention. Widespread use of smartphones, along with the ease of access to a variety of information through different applications, improves the process of training. Also, this approach is effective in maintaining the individuals' health, controlling the related condition, and preventing risky behaviors (31).

An educational program on pre-eclampsia increased the awareness of high-risk women significantly, which is reflected in improving certain pregnancy outcomes like Apgar scores and mean diastolic blood pressure. Intriguingly, self-monitoring, which is represented in adherence to the provided information and recommendations, was also increased upon improving awareness on pre-eclampsia. For instance, informed mothers control their mean diastolic blood pressure with more caution compared with those without educational intervention (26). In order to guarantee adherence and commitment of patients to a self-monitoring process, an educational program preferably includes physicians, obstetricians, and other health care providers (26).

Studies have shown that raising awareness is strongly associated with early detection of pregnancy risks, which, in turn, can prevent dangerous complications (21, 30). In a study from Ethiopia, Wassihun et al. (31) found that mothers who participated in antenatal care were 1.26 times more likely to be aware of the symptoms of labor risk than those who were not. It was also found that the participants who gave birth in specialized health centers were 3.57 times more aware of the danger signs of childbirth than those who had labor at home, which is mainly due to the information given by the medical staff. Another study in Australia also supported that increasing the coverage of prenatal care and the education level of women elevates mothers' knowledge about the symptoms of childbirth risks. In another study, it was observed that the level of awareness was significantly associated with age, the level of education, employment status, and monthly household income of pregnant women (28). Therefore, the importance of raising awareness in pregnant women has been indicated previously, and the need for interventions to increase awareness is, today, felt more than ever.

Parsa et al. used a mobile application to educate pregnant women on pre-eclampsia. The results of this study emphasized the positive and significant effect of educational interventions on pregnant women's awareness about the symptoms of preeclampsia. This would reduce the risk of further serious complications of preeclampsia. Other studies also showed increased awareness of pregnant women undergoing educational intervention in the field of preeclampsia and gestational hypertensive disease (24–26, 29).

While education increases the ability of women to recognize pre-eclampsia and prevent related complications, being more informed is not associated with anxiety exacerbation (24). Pregnant women were very satisfied with receiving a pamphlet containing information on lethal potential of pre-eclampsia because their knowledge was increased without worsening the anxiety during the critical period of pregnancy (27). An HDP pamphlet developed patients' knowledge about future risks of health and pregnancy in a population of women with recent HDP diagnosis with the anxiety level remained unchanged. This knowledge that lasted at least for 1 month also elevated the perception of long-term heart disease. The authors concluded that lifestyle behavior is changed toward decreasing cardiovascular risk in this way (28).

It has been previously shown that maternal knowledge and awareness strongly affect the health of the child, which can be partly attributed to differences in prenatal care and reduction of adverse delivery outcomes (32). It is better to initiate educational programs as early as possible in pregnant women, and it should maintain for at least 3 months after partum (26). Different studies have investigated the effects of educational programs on pregnant women with different characteristics. Pregnant women of 20 to 32 weeks were recruited for receiving an educational tool in one study (24). Another study included postpartum women between 4 weeks and 18 months for educational intervention (28). A sample of 100 pregnant women who were hospitalized for suspected or proven pre-eclampsia was studied in the other study (27). In some studies, the duration of intervention was a 1-month period (11), whereas a 2-h educational session on pre-eclampsia was given to high-risk pregnant women in another study (26). With the implementation of educational programs, the health status of mothers and their babies are improved due to appropriate actions. This shows the importance of educational programs to reduce the risks and complications around pregnancy (26). However, some hurdles are identified that hamper effective use of health information during pregnancy, such as mistrust between patients and health care providers, and lack of suitable communication between them due to bad attitude of the latter (33).

One important strength of the present study is that it is the first systematic review on the effect of educational intervention on knowledge of pregnant women's knowledge about HDP. However, since the studies were conducted in three Asian countries and Canada, it is not possible to generalize the results to other populations and ethnicities.

CONCLUSION

Altogether, the included studies showed that educational intervention strategies have a positive and significant impact on increasing the awareness of pregnant women about hypertensive disorders of pregnancy, which may help to reduce the severe complications caused by the disease. Future RCTs may compare the impact of various types of educational interventions on pregnant women.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

KG and MD performed the search. AA and SK performed first screening. MS and HG performed second screening. KG and YS evaluated risk of bias. NN and MK drafted the manuscript. AK and SH revised the manuscript. ND designed, critically revised, and supervised the course of drafting the article. All authors contributed to the article and approved the submitted version.

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The protocol of this systematic review is available at https://archive.org/details/osf-registrations-gcs5r-v1.

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Maternal Hypercholesterolemia May Involve in Preterm Birth

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Maternal hypercholesterolemia during pregnancy is associated with an increased risk of preterm birth which is defined as <37 weeks of complete gestation. However, the underlying mechanism for the association between hypercholesterolemia and preterm birth is not fully understood. Macrophage, as one of the largest cell types in the placenta, plays a very critical role in mediating inflammation and triggers labor initiation. Here, we hypothesize that macrophages can uptake maternal excessive cholesterol leading to its accumulation, resulting in a breach of the immune tolerance and precipitating labor.

Keywords: preterm birth, macrophage, cholesterol, low-density lipoprotein receptor, inflammation

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INTRODUCTION

The hydrophobic lipid, cholesterol (C27H46O), first isolated from human gallstones more than two centuries ago, plays a critical role in maintaining normal human physiology. Disruption in cholesterol metabolism can cause congenital human diseases (such as Familial hypercholesterolemia, Tangier disease, Schnyder corneal dystrophy) and acquired diseases (such as atherosclerosis, cardiovascular disease, and Alzheimer's disease) (1).

Cholesterol is a structural component and presents in every cellular membrane, which is also essential for embryonic and fetal development. Burgeoning evidence supports the role of cholesterol in parturition with very high level of cholesterol in pregnant women being associated with an increased risk of preterm birth (PTB) in comparison to women with moderate cholesterol level (2, 3). A meta-analysis involving 13,025 pregnant women found that maternal dyslipidemia during pregnancy, either the elevated total cholesterol or triglycerides, was associated with an increased risk of PTB (4). Besides, the cholesterol transporters such as ATP-binding cassette (ABC)-transporters, ABCA1 and ABCG1 are involved in parturition (5, 6) as evidenced by the study showing the association between abnormal expression of ABCA1 to the dysregulation of placental lipid metabolism and development of spontaneous PTB (7).

PTB is defined as delivery prior to 37 weeks gestational age. With an estimated global incidence of ∼15 million per year, PTB constitutes the leading cause of neonatal morbidity and mortality worldwide (8), thereby putting a tremendous emotional and economic burden on society. Premature infants are also at risk of developing immediate complications like respiratory distress syndrome, sepsis, intraventricular hemorrhage, necrotizing enterocolitis, hypothermia, hypoglycemia, hyperbilirubinemia and long-term morbidity like retinopathy of prematurity, neurodevelopmental impairment, and cerebral palsy (8). However, pathophysiology of initiation of labor is poorly understood, the therapeutic strategies of prevention and treatment of PTB is limited. Cholesterol from pregnant woman with hypercholesteremia may get transported into placenta and accumulate, which triggers an inflammation response and results in PTB. Therefore, it is important to illustrate underlying mechanism of maternal dyslipidemia that can lead to premature delivery, with an aim of providing novel therapeutic target.

PRESENTATION OF THE HYPOTHESIS

Massive amounts of cholesterol are needed for growth. Fetuses have two sources of cholesterol, *de novo* synthesized cholesterol and exogenous cholesterol from maternal circulation *via* the placenta. Well-documented evidence has shown that fetus procure cholesterol from their mother (9). Newborns have a large amount of plant sterols, the content of which is about 40–50% of that in the mother (10). Since plant sterols are only obtained from the diet, their presence in fetal serum indicates their vertical transmission. Substantial cholesterol is also present in fetus who are unable to synthesize cholesterol due to genetic abnormalities (11, 12). A recent study also found that there was substantial uptake of cholesterol from mother (measured as difference in the arterial-venous concentrations) by the fetus using a 4-vessel sampling method (13). Transfer of maternal cholesterol to the embryo as well as the fetus was also confirmed in mice (14). Maternal cholesterol must cross trophoblast barrier of placenta to reach the fetal circulation (15), suggesting entry of maternal cholesterol through placenta.

The various cell types in the placental disc include trophoblasts, macrophages, connective tissue fibroblasts and vascular cells. It is unclear which cell type in the placenta contributes to uptake of cholesterol. In maternal circulation, the majority of cholesterol is in the form of LDL-cholesterol or HDL-cholesterol, which can be uptake by trophoblast of placenta *via* its low-density lipoprotein receptor (LDLR) and scavenger receptor class B type I (SR-B1), respectively (9). Macrophages take up native and modified (for example, oxidized) LDL-cholesterol *via* micropinocytosis, phagocytosis, or scavenger receptor-mediated pathways (including *via* SR-B1, lectin-like oxidized LDL receptor 1, and CD36) (16). Macrophages were reported to express multiple scavenger receptors for uptake of LDL, which promotes the cellular accumulation of cholesterol (17). Scavenger receptors constitute a heterogeneous family of receptors including CD36 and SR-B1. CD36 is a membrane glycoprotein that is expressed on various types of cells, which can bind to multiple ligands and mediate the endocytosis of LDL (18). SR-B1 can mediate cholesteryl esters selective uptake and the bi-directional flux of free cholesterol (19). Peroxisome proliferator–activated receptors (PPARs) and liver X receptors (LXRs) are members of the nuclear receptor superfamily of transcription factors that play a key role in regulating the expression of scavenger receptors of macrophages (20). PPARγ is required for placental development and regulates essential placental functions (21), which may also be a drug target for complicated pregnancy (22). LXR was also reported to be an important factor in early-pregnancy lipogenesis which is necessary to protect against abnormalities in fetoplacental lipid homeostasis (23). However, whether PPARγ and LXRs involve in the uptake of cholesterol by macrophages in the placenta needs more studies.

Besides, cholesterol can also transfer from one cell type to adjacent different cell types (24), raising a possibility that the excess cholesterol of trophoblast may be a result of cholesterol accumulation by adjacent macrophage. Down-regulation of lipids associated receptors of placenta such as LDLR, SR-B1 results in decreased uptake of cholesterol by placental from maternal circulation (5). The mRNA expression of lipoprotein receptors, including LDLR and very low-density lipoprotein receptor (VLDLR) was significantly increased in placenta from hypercholesterolemic women as comparison to the control group (25). A plausible explanation can be the uptake of LDL-cholesterol by placenta may lead to upregulation of lipoprotein receptors, which in turn, results in uptake of LDL-cholesterol in placenta macrophages.

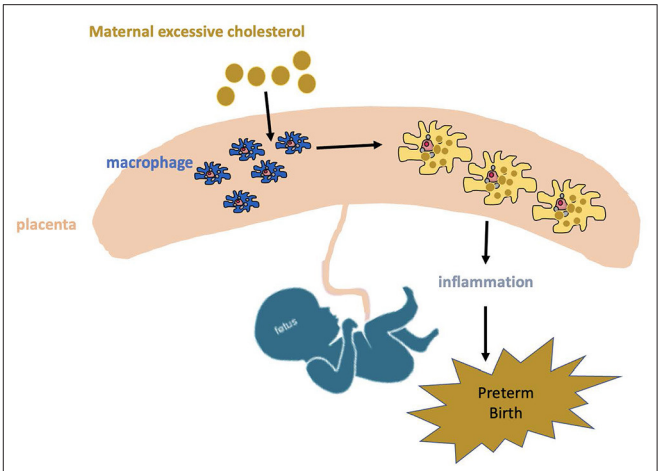

FIGURE 1 | Potential mechanism of maternal hypercholesterolemia contributing to preterm birth. Excessive cholesterol from mother with hypercholesterolemia will be transported into placenta and accumulates in macrophages, which will increase inflammation response and consequently trigger preterm birth.

A large body of literature shows the accumulated LDL-cholesterol in tissues can be modified to function as a ligand for macrophage pattern recognition receptors, including Toll-like receptors (TLRs), thereby directly triggering pro-inflammatory signaling pathways (26). Besides, accumulation of LDL-cholesterol in macrophages through endocytosis can also trigger TLR signaling (27, 28). Production of cytokines and chemokines may be amplified by increased TLR, amplifying the inflammatory process (27, 28).

Macrophages are a major type of leukocytes in the placenta and play a critical role throughout pregnancy (29). These placental macrophages support a variety of processes essential for successful pregnancy such as remodeling of the uterine connective tissues and blood vessels, regulation of trophoblast implantation, immune-tolerance toward fetal antigens, immunomodulation of neighboring leukocytes and initiation of parturition (30). Besides, placental macrophages are an important component for suppression of maternal immunologic response to the allogenic placenta and fetus due to its decreased ability to present antigens to T cells during pregnancy. Near term, placental macrophage activity switched to inflammation state contributes to parturition through production of pro-inflammatory cytokines and prostaglandin E2 (31), which in turn break the immune tolerance and initiate parturition. Accumulation of cholesterol in macrophages can trigger pro-inflammatory signaling pathways (26). It is well-validated that pregnant women with hypercholesterolemia

are associated with increased risk of PTB (2, 3, 32). Therefore, we hypothesize excessive cholesterol from the mother with hypercholesterolemia will be transported into the placenta and accumulate in macrophages, which will subsequently increase the inflammation, triggering PTB (**Figure 1**).

TESTING THE HYPOTHESIS

We will design some experiments to test this hypothesis. ① C57BL/6 male and female mice will be randomly given normal chow diet or 5% high cholesterol diet for 2–4 months (need to be optimized). Set up timed breeding and monitor the timing of parturition. At the endpoint of the experiment, mice will be sacrificed and blood, placenta will be collected. We will measure cholesterol levels in blood and placenta. We will isolate macrophage in placenta and measure lipids levels and the expression of cholesterol-uptake associated receptors including VLDLR, LDLR, CD36, and SR-B1. ② We will isolate macrophages from placenta by magnetic-activated cell sorting (MACS), then detect the cytokine, lipids and inflammation related gene expression in the absence or presence of the cultured macrophages with high LDL-cholesterol and oxidized LDL-cholesterol. ③To investigate the cholesterol uptake from the mother to macrophages in the placenta, the pregnant female mice will be injected with APOB-labeled particle ([^{125}I]-LDL) or LDL-cholesterol ([^{3}H]-CE-LDL) *via* tail veins at 17.5 days post coitum (dpc). Macrophages in the placenta will be isolated at 30 min, 1, 2, and 4 h after injection. Radioactivity in the homogenate of macrophages will be measured by γ-counting.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

JinC and JiaC conceived the idea. JinC and FL wrote the manuscript. JiaC, LH, and JinC collected and read the literature. All authors read and approved the final manuscript. All authors contributed to the article and approved the submitted version.

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Pregnant outcomes of critically ill pregnant patients with pulmonary hypertension: A multicenter retrospective study

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Objective: To identify the pregnancy outcomes and risk factors of critically ill pulmonary hypertension (PH) patients with intensive care unit (ICU) admission.

Methods: The multicenter, retrospective cohort study was performed on 60,306 parturients from January 2013 to December 2018 in China. Diagnosis of PH was based on the estimation of systolic pulmonary arterial pressure (sPAP) *via* echocardiography. Patients were stratified by sPAP into three groups, mild (30–50 mmHg), moderate (51–70 mmHg), and severe (>70 mmHg). The primary outcome was major adverse cardiovascular events (MACE), defined as a composite of in-hospital death, heart failure, and sustained arrhythmias requiring treatment. The secondary outcome was fetal adverse clinical events (FACE), a composite of fetal/neonatal death, prematurity, small birth weight, and fetal distress.

Results: A total of 181 pregnant patients were enrolled, including 101 patients with mild PH, 31 with moderate PH, and 49 with severe PH. The maternal median age was 32 (27, 35) years and 37% were nulliparous. The MACE occurred in 59 (59/181, 32.6%) women, including in-hospital death in 13 (13/181, 7.2%), heart failure in 53 (53/181, 29.3%), and sustained arrhythmias in 7 (7/181, 3.9%). The incidence of FACE was as high as 66.3% (120/181). Compared with mild and moderate PH patients, patients with severe PH had a significantly higher mortality rate (22.4 vs. 1.51%, $P < 0.001$) and MACE incidence (51.0 vs. 25.8%, $P = 0.001$). Although the incidence of FACE in severe PH was slightly higher than that in mild to moderate PH, there was no significant difference (69.4 vs. 65.1%, $P = 0.724$). PH complicated with left heart disease (OR = 4.365, CI: 1.306–14.591), elevated N-terminal pro-B-type natriuretic peptide (NT-proBNP) level (OR = 1.051, CI:1.015–1.088), and sPAP level estimated by echocardiography (OR = 1.021; CI: 1.003–1.040) were independently associated with MACE in multivariable regression ($P < 0.05$). Increased risk of FACE was noted for PH patients combined with eclampsia/preeclampsia (OR = 6.713; CI: 1.806–24.959).

Conclusion: The incidence of MACE and FACE remained high in critically ill pregnant patients with PH, particularly moderate and severe PH in China. Further studies are warranted to identify subsets of women with PH at lower pregnant risks and seek more effective therapy to improve pregnancy outcomes.

KEYWORDS

pulmonary hypertension, pregnancy, pregnant outcomes, critical care, China

Introduction

Pulmonary hypertension (PH) is a complex and devastating disease often leading to severe right heart failure and death. Women with PH are usually advised to avoid pregnancy because it is known to be associated with high maternal mortality (even up to 30–56%), as well as an extremely high incidence of fetal adverse clinical events (33–100%) (1–3). In reality, despite adequate counseling, some women with PH still chose to take great risks to get pregnant or continue unplanned pregnancies. In addition, recent data from the real world show that the incidence of pregnancy in women with PH is increasing, which may be due to the improvement in the diagnosis and treatment, so that more female patients with PH could survive to child-bearing age, and even have a near-normal life (4, 5).

Advances in the management of PH and pregnancy have significantly improved the pregnancy outcome of patients with PH. Recently, a series of studies, including a large national contemporary data set in the United States and a retrospective study from China, have reported lower mortality (0.8–6.4%) of PH patients with pregnancy than previously reported (6). Therefore, the individualized risk-based approach may be more appropriate for pregnancy in PH than the most recent guidelines recommendation to avoid pregnancy in all these patients. As most deaths occurred postpartum, the intensive care unit (ICU) has become the main battlefield for rescuing critically ill pregnant women. However, there are limited data on pregnancy outcomes and risk factors of critically ill PH patients admitted to the ICU.

The aim of this study was to investigate maternal and fetal outcomes in PH women with ICU admission. The clinical characteristics, complicated diseases, type of anesthesia, mode of delivery, and medication were evaluated, as well as the risk factors associated with postpartum maternal major adverse cardiovascular events (MACE) and fetal adverse clinical events (FACE).

Abbreviations: APACHE II score, Acute Physiology, Age and Chronic Health Evaluation II score; BMI, body mass index; CHD-PH, pulmonary hypertension complicated with congenital heart disease; cTnI, cardiac troponin I; CRP, C-reactive protein; CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation; FACE, fetal adverse clinical events; HELLP syndrome, hemolysis, elevated liver enzymes, and low platelets syndrome; ICU, intensive care unit; iPH, idiopathic pulmonary hypertension; LHD-PH, pulmonary hypertension complicated with left heart disease; M, median; MACE, major adverse cardiovascular events; MAP, mean arterial pressure; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; oPH, pulmonary hypertension associated with other disease; PA, pulmonary artery; PaO_2/FiO_2, the ratio of arterial oxygen partial pressure to fractional inspired oxygen; PH, pulmonary hypertension; Q1, the first quartile; Q3, the third quartile; SOFA score, sequential organ failure assessment score; sPAP, systolic pulmonary arterial pressure estimated *via* echocardiography.

Methods

Study design and participants

The multicenter retrospective study was conducted at three provincial maternal referral centers, including Shandong Provincial Hospital Affiliated to Shandong First Medical University, Taishan Hospital Affiliated to Shandong First Medical University, and Binzhou Medical University Hospital. All pregnancies including miscarriages, ectopic pregnancies, terminations, and completed pregnancies were enrolled. The pregnant patients with PH consecutively admitted to the ICU from January 1, 2013 to December 31, 2018 were included and analyzed. Patients with more than 20% data missing or key data missing were excluded (see Figure 1).

Data collection

All data were extracted from the electronic medical system. Two clinical researchers reviewed the electronic medical records and collected the data, then a third researcher determined any differences between the interpretations of the two primary reviewers. For patients with readmission during the study period, data from the first admission were presented. Survival after discharge was obtained by telephone interviews.

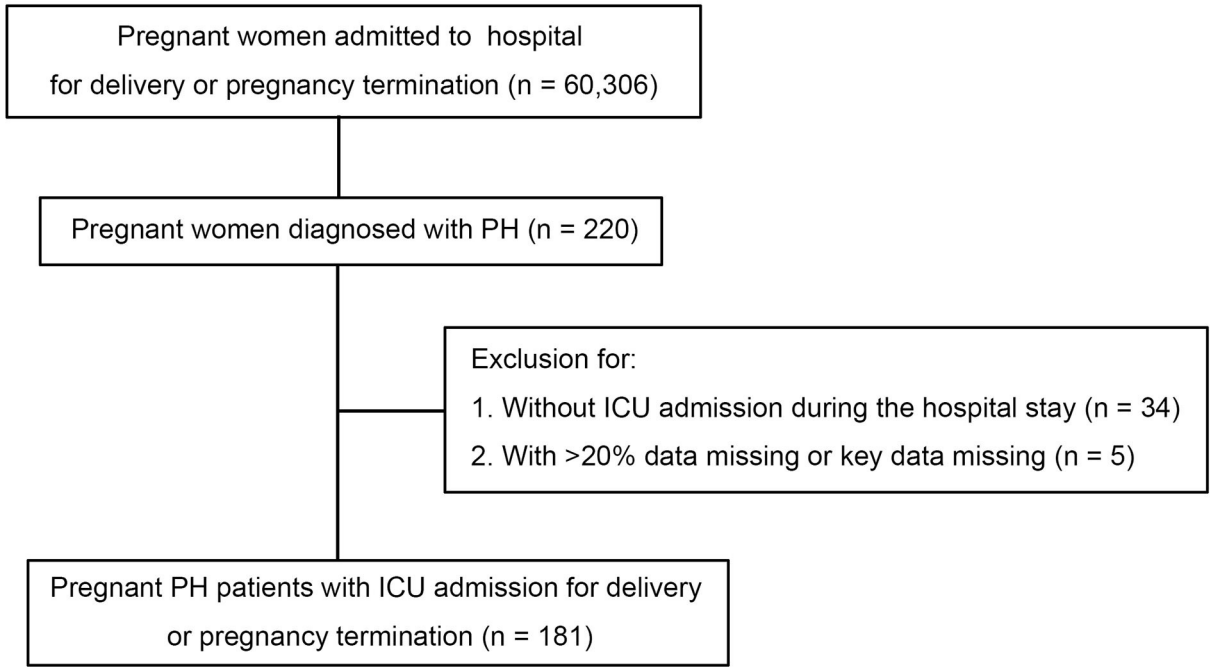

FIGURE 1
Study population and process of inclusion. ICU, intensive care unit; PH, pulmonary hypertension.

Diagnostic criteria and definitions of clinical parameters

Diagnosis of PH was based on the estimation of systolic pulmonary arterial pressure (sPAP) *via* echocardiography. When patients were admitted, echocardiography was performed by a qualified sonographer as described in the 2015 ESC/ERS guideline (3). Patients were stratified by sPAP into three groups, mild (30–50 mmHg), moderate (51–70 mmHg), and severe (>70 mmHg) (2). In addition, patients were divided into four groups according to the related disease: iPH, patients with an initial diagnosis of idiopathic PH before this admission and without any known cause of PH; CHD-PH, patients with a previous history of congenital heart disease; LHD-PH, patients with a history of left ventricular systolic dysfunction caused by valvular disease, cardiomyopathy, or acquired left heart outflow tract obstruction, but not congenital structural abnormality; oPH, PH caused by other diseases. For more definitions see Supplementary material 1.

Outcomes

The primary outcome was MACE, defined as a composite of in-hospital death, heart failure, and sustained arrhythmias requiring treatment (4, 7). The secondary outcome was FACE, a composite of fetal/neonatal death, prematurity, small birth weight, and fetal distress (8).

Ethical approval

Given the retrospective design of the study, which was based on data extracted from the electronic medical system, written informed consent was not required. All the procedures performed in this study were in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This study was registered in the Chinese Clinical Trial Registry and was approved by the Ethics Committee of Shandong Provincial Hospital (Registration number: ChiCTR1900020624).

Statistical analysis

The distributions of variables were examined with Kolmogorov–Smirnov tests. Continuous data were expressed as mean ± standard deviation or medians (interquartile range, IQR) as appropriate. Groups were compared by student *t*-tests or ANOVA analysis if they obey a normal distribution. If not, they were compared by Mann-Whitney U-tests or Kruskal-Wallis tests. Categorical data were expressed as numbers (percentages) and were compared by the chi-square test or

TABLE 1 Baseline characteristics of pregnant women based on PH severity diagnosed *via* echocardiography.

Variable	Total ($n = 181$)	Mild PH ($n = 101$)	Moderate PH ($n = 31$)	Severe PH ($n = 49$)	*p*-value
Age, years [M, (Q1, Q3)]	32 (27, 35)	29 (33, 37)	26 (31, 37)	24 (30, 34)	0.014
≤25 y (*n*, %)	34 (18.8)	13 (12.9)	4 (12.9)	17 (34.7)	
25-35 y (*n*, %)	92 (50.9)	51 (50.5)	17 (54.8)	24 (49.0)	
≥35 y (*n*, %)	55 (30.4)	37 (36.6)	10 (32.3)	8 (16.3)	
Nulliparous (n, %)	67 (37.0)	32 (31.7)	11 (35.5)	24 (49.0)	0.081
BMI, kg/m^2	26.8 (23.8, 30.9)	28.2 (25.0, 32.6)	26.5 (23.8, 29.6)	24.8 (22.4, 27.7)	0.000
Diagnosis made (*n*, %)					0.096
Before pregnancy	120 (66.3)	60 (58.6)	24 (77.4)	36 (73.5)	
During pregnancy	61 (33.7)	41 (40.6)	7 (22.6)	13 (26.5)	
Treatment (*n*, %)					
Targeted PH therapy	0 (0)	0 (0)	0 (0)	0 (0)	NS
Anticoagulation	2 (1.1)	1 (1.0)	1 (3.2)	0 (0)	0.452
Gestational week on admission, weeks [M, (Q1, Q3)]	35 (32, 37)	36 (32, 38)	36 (33, 38)	34 (31, 37)	0.112
Saturation, % [M, (Q1, Q3)]	100 (98, 100)	100 (98, 100)	100 (97, 100)	100 (98, 100)	0.981
MAP, mmHg [M, (Q1, Q3)]	92.0 (82.8, 108.8)	102.3 (82.8, 117.7)	88.7 (80.3, 99.3)	89.0 (79.8, 100.3)	0.014
Hemoglobin, g/L [M, (Q1, Q3)]	114.0 (102.0, 124.0)	113.0 (101.0, 119.0)	111.0 (102.0, 127.0)	116.0 (105.0, 134.05)	0.001
Hematocrit, % [M, (Q1, Q3)]	35.2 (32.3, 37.7)	35.0 (31.8, 36.9)	33.8 (32.2, 38.0)	35.9 (32.9, 40.8)	<0.001
Platelets, $\times 10^9$ /L [M, (Q1, Q3]	193 (146, 230)	194.0 (147.0, 227.0)	218.0 (175.0, 281.0)	178.0 (115.0, 219.0)	0.031
D-dimer, mg/L [M, (Q1, Q3)]	1.69 (1.02, 3.38)	2.2 (1.3, 3.7)	1.4 (0.9, 1.9)	1.3 (0.6, 4.0)	0.006
CRP, mg/L [M, (Q1, Q3)]	4.38 (2.33, 13.2)	4.5 (2.7, 13.7)	3.8 (1.7, 11.2)	4.9 (2.2, 15.6)	0.473
NT-proBNP, pg/ml [M, (Q1, Q3)]	490.6 (185.0, 1368.0)	424.7 (184.3, 1056.5)	495.4 (58.4, 1505.0)	595.7 (295.1, 2038.0)	0.201
Heart failure (*n*, %)	75 (41.4)	27 (26.7)	17 (54.8)	31 (63.3)	<0.001
NYHA class (*n*, %)					<0.001
I	76 (42.0)	53(52.5)	12 (38.7)	11 (22.4)	
II	55 (30.4)	35 (34.7)	10 (32.3)	10 (20.4)	
III	36 (19.9)	13 (12.9)	4 (12.9)	19 (38.8)	
IV	14 (7.7)	0 (0)	5 (16.1)	9 (18.4)	
APACHE II	3 (2,4)	3 (2,4)	3 (2,4)	3 (2,5)	0.838
SOFA score [M, (Q1, Q3)]	1 (0, 2)	1 (0, 2)	1 (0, 2)	1 (0, 2)	0.576
Echocardiographic parameters					
sPAP, mmHg [M, (Q1, Q3)]	49.0 (41.0, 73.0)	42.0 (38.0, 46.0)	58.0 (53.0, 66.0)	91.0 (81.0, 105.0)	<0.001
Diameter of main PA, cm [M, (Q1, Q3)]	2.7 (2.41, 3.17)	2.7 (2.4, 3.0)	3.0 (2.2, 3.2)	3.2 (2.5, 3.7)	0.075
Complications (*n*, %)					
Hypertension	56 (30.9)	44 (43.6)	5 (16.1)	7 (14.3)	<0.001
Pre-eclampsia/eclampsia	49 (27.1)	40 (39.6)	5 (16.1)	4 (8.2)	<0.001
HELLP syndrome	1 (0.6)	1(1.0)	0 (0)	0 (0)	NS
Diabetes mellitus	14 (7.7)	10 (9.9)	1 (3.2)	3 (6.1)	0.594
Autoimmune disease	11 (6.1)	8 (8.9)	0 (0)	3 (6.1)	0.393
Liver damage	5 (2.8)	1 (1.0)	2 (6.5)	2 (4.1)	0.095
Kidney injury	9 (5.0)	5 (5.0)	1 (3.2)	3 (6.1)	0.901
Others	15 (8.3)	10 (9.9)	2 (6.5)	3 (6.1)	0.757

(Continued)

TABLE 1 (Continued)

Variable	Total ($n = 181$)	Mild PH ($n = 101$)	Moderate PH ($n = 31$)	Severe PH ($n = 49$)	p-value
Related diseases (n, %)					
iPH	33 (18.2)	23 (22.8)	4 (12.9)	6 (12.2)	0.099
CHD-PH	83(45.9)	34 (33.7)	14 (45.2)	35 (71.4)	<0.001
Eisenmenger syndrome	8 (4.4)	0 (0)	1 (3.2)	7 (14.3)	<0.001
Left-to-right shunts	29 (16.0)	11 (10.9)	4 (12.9)	14 (28.6)	0.075
LHD-PH	15 (8.3)	9 (8.9)	5 (16.1)	1 (2.0)	0.075
oPH	50 (27.6)	35 (34.7)	8 (25.8)	7 (14.3)	0.041
Length of hospital stay, days [M, (Q1, Q3)]	7 (5, 9)	7 (5, 9)	7 (5, 9)	7 (5, 10)	0.898
Length of ICU stay, days [M, (Q1, Q3)]	2 (2, 4)	2 (1, 3)	2 (2, 3)	3.5 (2, 5)	<0.001

APACHE II score, Acute Physiology, Age and Chronic Health Evaluation II score; BMI, body mass index; CHD-PH, patients with the previous history of congenital heart disease; CRP, C-reactive protein; HELLP syndrome: hemolysis, elevated liver enzymes, and low platelets syndrome; ICU, intensive care unit; iPH, patients with an initial diagnosis of idiopathic pulmonary hypertension before this admission and without any known cause of pulmonary hypertension; LHD-PH, patients with a history of left ventricular systolic dysfunction but not congenital structural abnormality; M, median; MAP, mean arterial pressure; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; oPH, pulmonary hypertension associated with other disease; PA, pulmonary artery; PH, pulmonary hypertension; Q1, the first quartile; Q3, the third quartile; SOFA score, sequential organ failure assessment score; sPAP, systolic pulmonary arterial pressure estimated via echocardiography.

Fisher's exact tests. Cut-off points were presented *via* receiver operating characteristic (ROC) curves. Risk factors for MACE and FACE were determined with univariate logistic regression and multivariate logistic regression. Odds ratios (OR) with 95% confidence intervals (CI) and the corresponding *P*-values were calculated for each risk factor. Risk factors for in-hospital maternal death were determined with univariate cox regression and multivariate cox regression. Hazard ratios (HRs) with 95% confidence intervals (CIs) and the corresponding *P*-values were calculated for each risk factor. Kaplan–Meier survival analysis was used to describe the relative risk of death and the log-rank test was used to compare the survival probability of each group. *P*-values were considered statistically significant if <0.05 (two-sided test). The variables that had >5% of values missing were excluded. Another missing data imputation was done using the Expectation-Maximization method. All statistical analysis was performed using SPSS 25.0 (IBM Corporation, Armonk, New York, USA).

Results

Patient characteristics

From January 2013 to December 2018, a total of 60,306 deliveries were performed at the three provincial maternal referral centers and 220 (3.65 per 1,000 births) had PH. Of patients with PH, 186 (84.5%) were admitted to ICU. Five patients were excluded for missing data. In the final analysis, 181 patients were included in this study. Among all the pregnant patients with PH, 49 (27.1%) cases had an sPAP above 70 mmHg, 31 (17.1%) cases had an sPAP between 50 and 70 mmHg, and 101 (55.8%) cases had an sPAP below 50 mmHg. The maternal median age was 32 (27, 35) years and 37% were nulliparous. In more than 65% of patients, the PH diagnosis was made before pregnancy. However, no patients received targeted therapy for PH before or during pregnancy. The median gestational age on admission was 35 (32, 37) weeks, and there were no differences in mild, moderate, and severe PH groups. On admission, the sign of heart failure was presented in more than one-third of the pregnant women. Overall, women with severe PH were associated with higher NYHA cardiac classification compared to those with mild and moderate PH ($P < 0.001$). It was found that iPH was present in 33 (18.2%) patients, CHD-PH in 83 (45.9%), LHD-PH in 15 (8.3%), and oPH in 50 (27.6%) patients. Further baseline characteristics are presented in Table 1.

Management and clinical characteristics of patients

Management of pregnant patients with PH is presented in Table 2. The median gestational age at delivery was 35 (32, 38) weeks. Cesarean section (CS) was performed in 174 patients (96.1%), of which 37 (20.4%) were emergency operations. Only 7 (3.9%) women delivered virginally. Compared with mild ($n = 20$, 19.8%) and moderated ($n = 6$, 19.4%) PH patients, more women with severe PH ($n = 24$, 49%) received general anesthesia. At ICU admission, compared with mild and moderate PH patients, the patients with sPAP >70 mmHg showed higher sequential organ failure assessment (SOFA) score, Acute Physiology, Age and Chronic Health Evaluation II (APACHE II) score, blood lactate level, D-dimer level, and more PaO_2/FiO_2 decrease. Further treatments are presented in Table 2.

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TABLE 2 Management of pregnant patients with pulmonary hypertension.

Variable	Total ($n = 181$)	Mild PH ($n = 101$)	Moderate PH ($n = 31$)	Severe PH ($n = 49$)	*p*-value
Delivery, weeks	35 (32, 38)	36 (32, 38)	37 (34, 38)	34 (31, 37)	0.185
Mode of delivery (*n*, %)					
Vaginal	7(3.9)	2 (2.0)	1 (3.2)	4 (8.2)	0.020
Cesarean section	174 (96.1)	99 (98.0)	30 (96.8)	45 (91.8)	0.021
Emergency cesarean section	37 (20.4)	16 (15.8)	6 (19.4)	15 (30.6)	0.232
Anesthesia (*n*, %)					
General	51 (28.2)	20 (19.8)	6 (19.4)	24 (49.0)	0.002
Epidural	19 (10.5)	10 (9.9)	5 (16.1)	4 (8.2)	0.538
Spinal	1 (0.6)	1 (1.0)	0 (0)	0 (0)	1.000
Epidural+Spinal	108 (59.7)	70(69.3)	19 (61.3)	19 (38.8)	0.003
On ICU admission					
APACHE II score, [M, (Q1, Q3)]	5 (3, 7)	4 (3, 6)	5 (3, 7)	6 (4, 8)	0.001
SOFA score [M, (Q1, Q3)]	1 (1, 2)	1 (1, 2)	1 (1, 3)	2 (1, 4.0)	0.023
Lactate, mmol/L [M, (Q1, Q3)]	1.2 (1.0, 1.7)	1.1(0.9, 1.4)	1.3 (0.9, 2.0)	1.5 (1.2, 2.8)	0.000
NT-proBNP, pg/ml [M, (Q1, Q3)]	451.2 (201.7, 1299.5)	440.7 (196.6, 1057.8)	730.1 (208.5, 1457.8)	548.7 (219.75, 1669.5)	0.532
cTnI, ng/ml [M, (Q1, Q3)]	10.7 (6.93, 22.1)	10.8 (6.9, 19.2)	9.1 (6.3, 16.1)	12.6 (5.9, 39.3)	0.489
PaO2/FiO2					<0.001
≤100 (*n*, %)	13 (7.2)	1 (1.0)	1 (3.2)	11 (22.4)	
100–300 (*n*, %)	109 (60.2)	66 (65.3)	17 (54.8)	26 (53.1)	
>300 (*n*, %)	59 (32.6)	34 (33.7)	13 (41.9)	12 (24.5)	
Hemoglobin, g/L [M, (Q1, Q3)]	106.0 (94.0, 120.0)	113.0 (101.0, 119.0)	111.0 (102.0, 127.0)	116.0 (105.0, 135.0)	0.113
Hematocrit, % [M, (Q1, Q3)]	32.8 (29.4, 35.8)	35.0 (31.8, 36.9)	33.8 (32.2, 38.0)	35.9 (32.9, 40.8)	0.003
Platelets, $\times 10^9$ /L [M, (Q1, Q3)]	177.0 (128.0, 228.0)	194.0 (147.0, 227.0)	218.0 (175.0, 281.0)	178.0 (115.0, 219.0)	0.222
D-dimer, mg/L [M, (Q1, Q3)]	3.71 (2.18, 7.72)	4.3 (2.7, 10.9)	2.6 (1.8, 4.1)	3.2 (2.0, 8.3)	0.033
CRP, mg/L [M, (Q1, Q3)]	5.63 (1.83, 21.7)	4.1 (1.5, 18.3)	16.4 (2.1, 35.5)	10.1 (3.2, 26.3)	0.173
Acute kidney injury (*n*, %)		6 (5.9)	1 (3.2)	3 (6.1)	1.000
Treatment (*n*, %)					
Inotropic agents	16 (8.8)	5 (5.0)	3 (9.7)	8 (16.3)	0.062
Vasoconstrictors	21 (11.6)	3 (3.0)	4 (12.9)	13 (26.5)	<0.001
Anticoagulation	121 (66.9)	72 (71.3)	22 (71.0)	27 (55.1)	0.099
Targeted PAH therapy	2 (1.1)	0 (0)	1 (3.2)	1 (2.0)	0.195
CRRT	9 (5.0)	3 (3.0)	1 (3.2)	5 (10.2)	0.187
ECMO	1 (0.5)	0 (0)	0 (0)	1 (2.0)	0.440
Fluid balance, ml [M, (Q1, Q3)]					
1st 24 h	−375 (−1321, 210)	−651 (−1686, 105)	−493 (−1058, 231)	−231 (−814, 233)	0.084
2nd 24 h	−386(−1202, 140)	−421 (−1406, 270)	−250 (−1249, 55)	−386 (−1104, 97.5)	0.965
3rd 24 h	−150 (−735, 480)	−97.5 (−658, 1125)	32.2 (−590, 384.5)	−211 (−777, 269)	0.592

APACHE II score, Acute Physiology, Age and Chronic Health Evaluation II score; cTnI, cardiac troponin I; CRP, C-reactive protein; CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; M, median; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PH, pulmonary hypertension; PaO_2/FiO_2, the ratio of arterial oxygen partial pressure to fractional inspired oxygen; Q1, the first quartile; Q3, the third quartile; SOFA score, sequential organ failure assessment score.

TABLE 3 Maternal and fetal/neonatal outcomes of women with PH diagnosed *via* echocardiography.

Variable	Total	Mild PH	Moderate PH	Severe PH	*p*-value
Maternal outcome					
Death	13 (7.2)	0 (0)	2 (6.5)	11 (22.4)	<0.001
During pregnancy (*n*, %)	0 (0)	0 (0)	0 (0)	0 (0)	1.000
Postpartum (<24 h) (*n*, %)	3 (1.7)	0 (0)	0 (0)	3 (6.1)	0.023
Postpartum (24 h−1 w) (n, %)	9 (5.0)	0 (0)	2 (6.5)	7 (14.3)	<0.001
Postpartum (>1 w, <6 w) (*n*, %)	1 (0.6)	0 (0)	0 (0)	1 (2.0)	0.439
Sustained arrhythmia (*n*, %)	7 (3.9)	1 (1.0)	3 (9.7)	3 (6.1)	0.033
Heart failure (*n*, %)	53 (29.3)	23 (22.8)	8 (25.8)	22 (44.9)	0.008
Thromboembolic event (*n*, %)	3 (1.7)	1 (1.0)	0 (0)	2 (4.1)	0.255
Postpartum hemorrhage (*n*, %)	8 (4.4)	6(5.94)	1 (3.2)	1 (2.0)	0.695
MACE (*n*, %)	59 (32.6)	24 (23.8)	10 (32.2)	25 (51.0)	0.001
Fetal/neonatal outcome					
Live births (*n*, %)	155 (85.6)	88 (87.1)	29 (93.5)	38 (77.5)	0.137
Prematurity (birth <37 w) (*n*, %)	108 (59.7)	62 (61.4)	16 (51.6)	30 (61.2)	0.598
Therapeutic abortion	17 (9.4)	8 (7.9)	1 (3.2)	8 (16.3)	0.154
Fetal death (*n*, %)	6 (3.3)	4 (4.0)	0(0)	2 (4.1)	0.727
Pregnancy loss (*n*, %)	23 (12.7)	12 (11.9)	1 (3.2)	10 (20.4)	0.087
Low birth weight (*n*, %)	63 (34.8)	35 (34.7)	10 (32.2)	18 (36.7)	0.928
Fetal distress (*n*, %)	9 (5.0)	6 (5.9)	1 (3.2)	2 (4.1)	1.000
Neonatal malformation (*n*, %)	1 (0.6)	0 (0)	1 (3.2)	0 (0)	0.167
Neonatal death (*n*, %)	3 (1.7)	2 (2.0)	0 (0)	1 (2.0)	1.000
FACE (*n*, %)	120 (66.3)	69 (68.3)	17 (54.8)	34 (69.4)	0.928

FACE, fetal adverse clinical events; MACE, major adverse cardiovascular events; PH, pulmonary hypertension.

Maternal and fetal outcomes

The in-hospital outcomes of these pregnant PH women are shown in Table 3. The MACE occurred in 59 (32.6%) women: in-hospital death in 13 (7.2%), heart failure in 53 (29.3%), and sustained arrhythmia in 7 (3.9%). Compared with patients with sPAP ≤70 mmHg, women with sPAP above 70 mmHg experienced significantly higher MACE (51.0 vs. 25.8%, $P = 0.001$). The related diseases and severity distribution of PH parturients who experienced MACE are shown in Figure 2. The in-hospital survival outcomes of these pregnant PH women are shown in Figure 3. Compared with mild and moderate PH patients, patients with severe PH had a significantly higher mortality rate (22.4%, $P < 0.001$). Of all the 13 in-hospital deaths, 1 died of pulmonary hypertension crisis and 12 died of heart failure. There were two deaths in patients with moderate PH. One patient (sPAP = 53 mmHg) died of valvular thrombosis-induced heart failure, which was due to previous aortic valve replacement, postpartum hemorrhage, and anticoagulant discontinuation. The other patient (sPAP = 70 mmHg) died of a sudden cardiac arrest. In addition, most patients died within 1 week postpartum (3 died within 24 h and 9 died within 24 h to 1 week postpartum), and one woman died 12 days after delivery. Moreover, a total of 168 patients were followed up for at least 1 year after discharge. During the follow-up,1 patient died of heart failure 116 days after discharge and one patient died of cerebral hemorrhage 110 days after discharge. Both the two patients had sPAP above 70 mmHg.

The FACE occurred in 120 (66.3%) women, including 17 (9.4%) therapeutic abortion, 6 (3.3%) fetal death, 3 (1.7%) neonatal death, 108 (59.7%) prematurity, 63 (34.8%) small birth weight, and 9 (5.0%) fetal distress. Although the incidence of FACE in patients with severe PH was slightly higher than that in patients with mild to moderate PH, there was no significant difference (69.4 vs. 65.1%, $P = 0.724$). Further maternal and fetal/neonatal outcomes are presented in Table 3.

Risk factors for maternal and fetal outcomes

The result of univariable logistic and cox regression is presented in Supplementary material 2. The result of multivariable logistic and cox regression is shown in Tables 4, 5. MACE was more likely to occur in patients with higher sPAP, higher NT-BNP level, higher lactate level, higher cTnI level, and lower PaO_2/FiO_2. Under the age of 25, heart failure on admission, acute kidney injury, LHD-PH, emergency

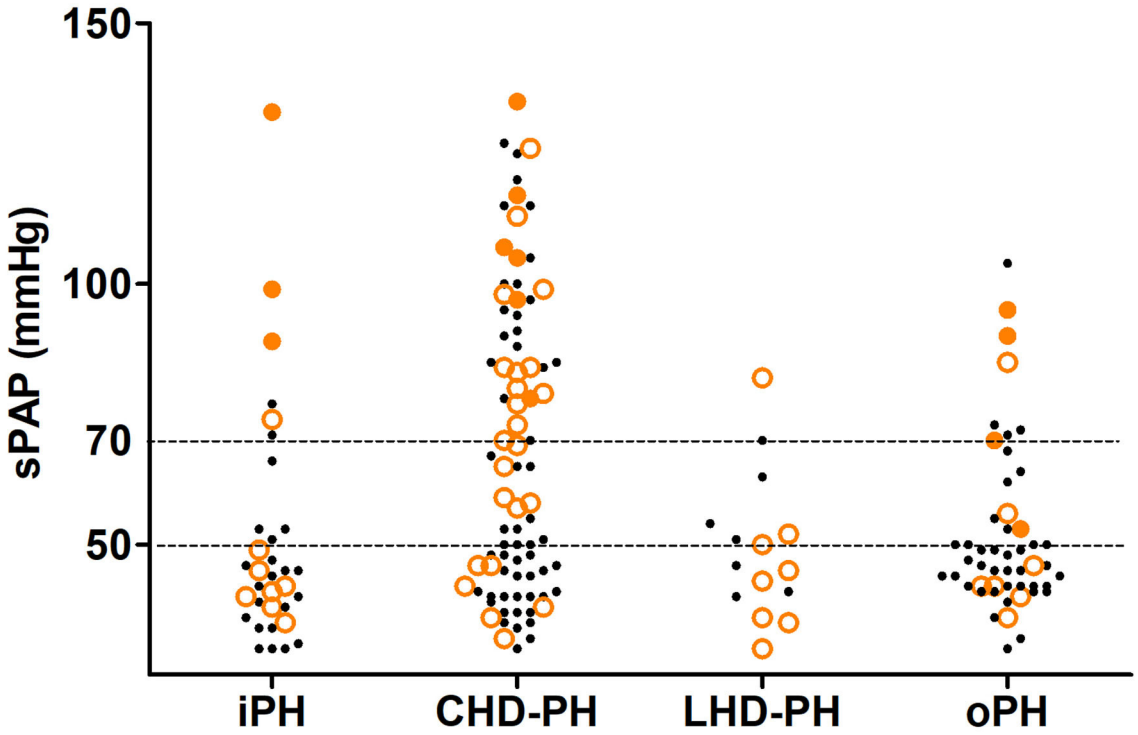

FIGURE 2
In-hospital outcome of the pregnancy and different severities of pulmonary hypertension in the study population based on the related disease. The small black dots represent the cases without MACE, the lager orange circles represent the cases that experience MACE, and the large orange dots represent the cases that experience in-hospital death. CHD-PH, patients with the previous history of congenital heart disease; iPH, patients with an initial diagnosis of idiopathic pulmonary hypertension before this admission and without any known cause of pulmonary hypertension; LHD-PH, patients with a history of left ventricular systolic dysfunction but not congenital structural abnormality; MACE, major adverse cardiovascular events; oPH, pulmonary hypertension associated with other diseases; sPAP, systolic pulmonary arterial pressure estimated *via* echocardiography.

cesarean section, and higher APECHE II and SOFA scores were considered possible risk factors for MACE. Patients in whom the FACE occurred had higher BMI, higher NT-proBNP, higher SOFA score, and lower PaO_2/FiO_2. Hypertension, eclampsia/preeclampsia, CHD-PH, and general anesthesia were all considered possible risk factors for FACE. According to the multivariable logistic regression analysis, the development of MACE was associated with the complication of left heart disease (OR = 4.365, CI:1.306–14.591), and elevated NT-proBNP level (OR = 1.051, CI:1.015–1.088) and sPAP level estimated by echocardiography (OR = 1.021; CI: 1.003–1.040). Combined with eclampsia/preeclampsia was considered to be a risk factor for FACE (OR = 6.713; CI: 1.806, 24.959). Delivery week >32 weeks was proved to be protective in FACE (OR = 0.056, CI: 0.007–0.444). According to the cox regression, in-hospital maternal death was much more likely to happen in patients with higher sPAP estimated by echocardiography (HR = 1.056; CI: 1.029–1.084), higher NT-proBNP level on admission (HR = 1.011; CI: 1.001–1.020) and higher lactate level on ICU admission (HR = 1.135; CI: 1.020–1.263). As presented in the ROC curves (see Supplementary material 3), the cut-off of sPAP, NT-proBNP on admission, and lactate level on ICU admission was 70 mmHg, 1,000 pg/ml, and 2.85 mmol/L, respectively.

Discussion

In this retrospective multicenter study, we analyzed clinical characters, complications, treatments, as well as maternal and fetal/neonatal outcomes of 181 pregnant PH women in the past 6 years. The incidence of MACE (32.6%) and FACE (66.3%) remained extremely high despite the continuous progress of treatment in recent years. Pregnant women with LHD-PH, high NT-proBNP levels, and higher sPAP levels were risk factors for the development of MACE. In addition, high sPAP (≥70 mmHg) estimated *via* echocardiography elevated NT-proBNP (≥1,000 pg/ml) on admission, as well as high lactate level (≥2.85 mmol/L) on ICU admission had a good predictive value for maternal death. Combined with eclampsia/preeclampsia was independently associated with FACE development.

Consistent with previous studies, patients with LHD-PH experienced the most MACE. There were 53.3% (8 out of

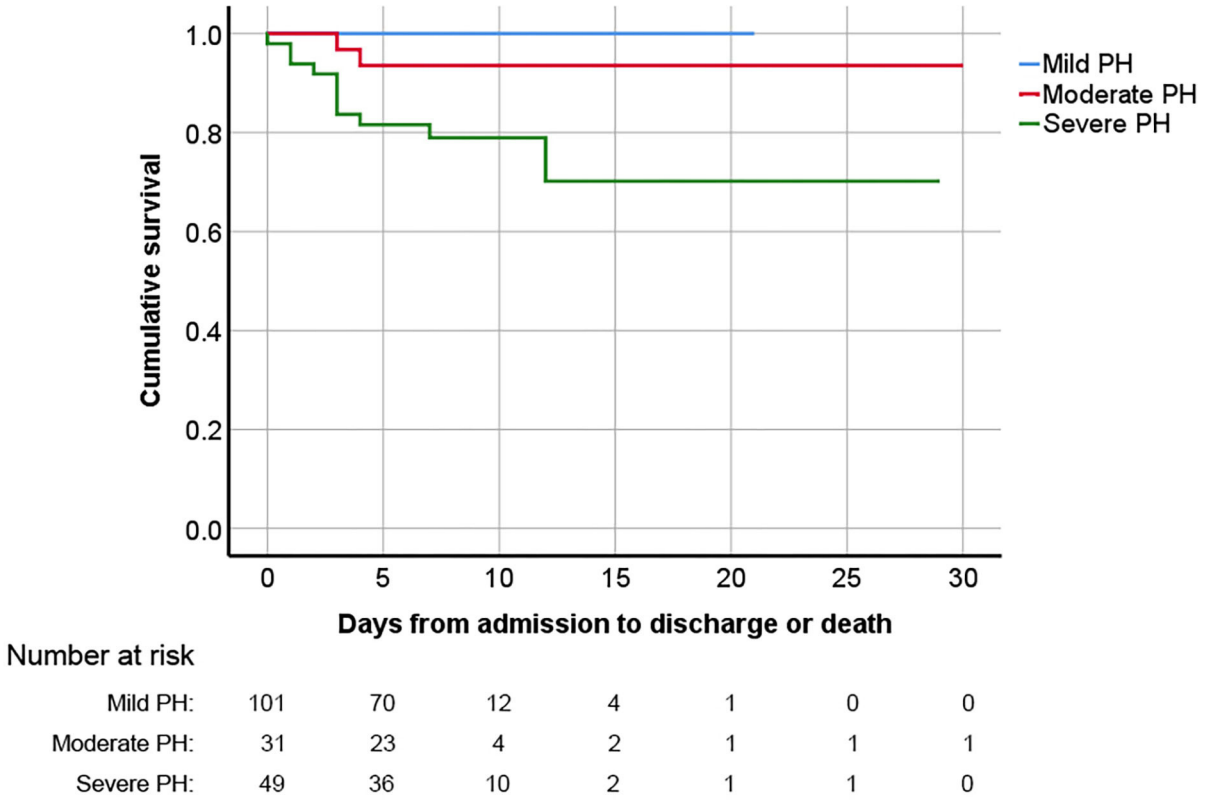

FIGURE 3
Kaplan–Meier survival analysis curve for pregnant women with PH diagnosed *via* echocardiography based on PH severity. PH, pulmonary hypertension.

15) LHD-PH patients who experienced MACE, which was much higher than the other three groups (34.9% in CHD-PH patients, 33.3% in iPH patients, and 22.0% in oPH patients). In a European registry of 1,321 pregnant women with cardiac disease, patients with cardiomyopathy, commonly combined with left ventricular dysfunction, had the most adverse cardiac events (9). Different from the systolic and diastolic capacity of right ventricular injury caused by long-lasting increased afterload, LHD-PH often occurred as a consequence of a passive filling pressure of the left heart, which was driven by left ventricular dysfunction and left atrium compliance loss (10, 11). After delivery, uterine contraction and increased blood volume would furtherly aggravate the condition. However, despite the relatively high incidence of adverse events, all of the LHD-PH women survived, and most of them underwent a successful delivery, which was consistent with previous reports (6, 12). The possible reason was that most of the underlying heart diseases were generally monitored and well-controlled before pregnancy, and most of the LHD-PH patients were in the mild to moderate PH group.

Pregnancy with PH has a high risk of death. Compared with the maternal mortality rate (18.3/100,000) in China in 2018, the mortality rate of pregnant patients complicated with PH increased by nearly 400 times in the present study. Similar to our study, higher mortality was also reported in other studies but showed a decreasing trend (1, 13, 14). A meta-analysis including 20 studies and 589 cases reported a pooled maternal mortality of 11.5%. The data from a European registry of 151 pregnant PH women showed a mortality of 3.3% within 1 week postpartum, and 4.6% during 6-month postpartum follow-up (2). In another study of 1,519 patients using the U.S. database data, the in-hospital maternal mortality was 0.8% (6, 15). The authors attributed this relatively lower maternal mortality to collaborative multidisciplinary team management, planned termination of pregnancy before 28 weeks, and preference for spinal or epidural anesthesia. Therapeutic abortion was also found helpful in other researches; however, the mode of delivery and anesthesia remained contentious (16). In this study, we also found that no death occurred in patients who terminated pregnancy before 28 weeks, including patients with severe PH in this study, suggesting that early termination of pregnancy might improve the prognosis of pregnant women with PH, but more real-world studies are warranted.

TABLE 4 Multivariable logistic regression of risk factors for MACE and FACE in pregnant patients with PH diagnosed *via* echocardiography.

Variable	Multivariable logistic regression	
	OR (95%CI)	*p*-value
MACE (*n* = 59, 32.6%)		
LDH-PH	4.365 (1.306, 14.591)	0.017
NT-proBNP	1.051 (1.015, 1.088)	0.005
sPAP	1.021 (1.003, 1.040)	0.025
FACE (*n* = 120, 66.3%)		
Delivery week greater than 32wks	0.056 (0.007, 0.444)	0.006
Combined with eclampsia/preeclampsia	6.713 (1.806, 24.959)	0.004

FACE, fetal adverse clinical events; LHD-PH, patients with a history of left ventricular systolic dysfunction but not congenital structural abnormality; MACE, major adverse cardiovascular events; NT-proBNP, N-terminal pro-B-type natriuretic peptide; sPAP, systolic pulmonary arterial pressure.

TABLE 5 Multivariable cox regression of risk factors for maternal mortality in pregnant patients with PH.

Variable	Multivariable cox regression	
	HR (95%CI)	*p*-value
In hospital maternal death (*n* = 13, 7.2%)		
sPAP	1.056 (1.029–1.084)	<0.001
NT-proBNP on admission	1.011 (1.001–1.020)	0.031
Lactate level on ICU admission	1.135 (1.020–1.263)	0.020

ICU, intensive care unit; NT-proBNP, N-terminal pro-B-type natriuretic peptide; sPAP, systolic pulmonary arterial pressure.

Although invasive hemodynamic measurements are still the gold standard for PH diagnosis, a detailed echocardiographic assessment of pulmonary artery pressure could help to identify patients at risk of PH. Accumulating evidence suggested a correlation between non-invasive and invasive data, but the reported results were not completely consistent (17, 18). For an individual patient, significant overestimation and underestimation might occur. Recent guidelines have suggested that although echocardiography could not provide a definitive diagnosis, it was of great significance in determining the probability of PH being present (19). In addition, for pregnant women with confirmed or moderate to severe PH, echocardiography might be more suitable for dynamic prediction and follow-up because of its non-invasive and convenient. Consistent with recent research (20), the level of sPAP measured by echocardiography was closely associated with mortality and morbidity of postpartum adverse events in pregnant PH women in our study. Furthermore, the optimal cut-off value of sPAP for predicting mortality was 70 mm Hg, which yielded sensitivity and specificity of 88.9 and 71.1%, respectively.

In this study, we found that pregnant PH women with high levels of NT-proBNP had higher mortality and more cardiac adverse events. NT-proBNP levels have also been included in the multiparametric risk assessment approach for PH outlined in PH guidelines (3, 21). In PH patients, NT-proBNP was secreted by the ventricular myocardium in response to transmural pressure, volume overload as well as hypoxia (22). As demonstrated in a previous study including PH patients both newly diagnosed and receiving long-term treatment, change in NT-proBNP level was correlated to the changes in right ventricular function (23). However, data supporting the use of NT-proBNP risk thresholds in assessing pregnancy risk in PH are limited and inconsistent. Further studies are required to confirm the prospective use of NT-pro BNP in this field.

We noticed a high FACE incidence rate of 66.3% in our study. Compared with a recent meta-analysis that reviewed 589 parturients and 610 pregnancies in 20 studies, there are similar pregnancy loss rate (12.7 vs. 12.6%) and a higher prematurity rate (59.7 vs. 51.7%) in this study (16). Planned early delivery was widely applied to avoid adverse events in our study, which was a possible reason for this high prematurity rate. In our study, PH combined with eclampsia/preeclampsia was associated with FACE. One explanation for poor fetal outcomes of PH patients was limited placental development due to decreased cardiac output (2). Placental disease due to vascular endothelial injury was also recognized as the main cause of fetal restriction and stillbirth in eclampsia/preeclampsia. As reported, women with PH were more likely to experience eclampsia, which was a risk factor for both maternal and fetal adverse events (6, 24). Furthermore, pulmonary artery pressure would significantly increase in the third trimester, and most of the patients with severe PH had NYHA class decline by 1 or 2 (25). Considering maternal and fetal safety, despite the patients' strong desire of continuing pregnancy, most of them were advised to terminate the pregnancy early. The specific influence of PH on placental development remained unclear. Further research on fetal outcomes was still needed.

The major limitation of the study was related to its retrospective nature. In this study, all data were extracted from the electronic medical system, and some of the data were incomplete or unavailable. In addition, the diagnosis of PH was not made with a right heart catheterization. It is inevitable to overestimate or underestimate the value of sPAP in an individual patient leading to misdiagnosis and inappropriate treatment. The interpretation of our data must take into account the limitations of echocardiography in the diagnosis of PH. Thus, all conclusions must be drawn with caution.

In conclusion, maternal mortality remained high despite advanced treatment, and the incidence of MACE and FACE was also very high in this multicenter data set of critically ill

pregnant women with PH in China. PH patients with left heart disease, increased sPAP estimated by echocardiography, and elevated NT-proBNP are at high risk of cardiac adverse events and should receive closer medical monitoring. If necessary, planned early delivery should be considered to avoid sudden deterioration of cardiac function. However, further studies are warranted to identify subsets of women with PH at lower pregnant risks and seek more effective therapy to improve pregnancy outcomes.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Medical Ethics Committee of Provincial Hospital Affiliated to Shandong University. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Author contributions

YC and MM contributed to conception and design of the study. GQ, XY, HZ, FZ, and TW contributed to data acquisition and outcome measure. LZ and YC performed the statistical analysis. LZ wrote the first draft of the manuscript. YC, MM, and JS revised the manuscript critically. All authors contributed to manuscript revision, read, and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.872833/full#supplementary-material

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Association between parity and markers of inflammation: The multi-ethnic study of atherosclerosis

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Introduction: Multiparity has been associated with increased risk of cardiovascular disease (CVD). Inflammation may be a mechanism linking parity to CVD. We investigated the association between parity and later-life markers of inflammation.

Methods: We studied 3,454 female MESA participants aged 45–84, free of CVD, who had data on parity and inflammatory markers. Parity was categorized as 0 (reference), 1–2, 3–4, or ≥5. Linear regression was used to evaluate the association between parity and natural log-transformed levels of fibrinogen, D-dimer, GlycA, high sensitivity C-reactive protein (hsCRP), and interleukin-6 (IL-6).

Results: Mean age was 62 ± 10 years. The proportion of women with nulliparity, 1–2, 3–4, and ≥5 live births were 18, 39, 29, and 14%, respectively. There was no association between parity and fibrinogen. Women with grand multiparity (≥5 live births) had 28, 10, and 18% higher levels of hsCRP, IL-6 and D-dimer, respectively, compared to nulliparous women, after adjustment for demographic factors. After additional adjustment for CVD risk factors, women with 1–2 and 3–4 live births had higher hsCRP and women with 1–2 live births had higher GlycA.

Conclusion: In this diverse cohort of middle-to-older aged women, we found that higher parity was associated with some inflammatory markers; however, these associations were largely attenuated after adjustment for CVD risk factors. There was no clear dose-response relationship between parity and these inflammatory markers. Future studies are needed to evaluate how inflammation may influence the link between parity and CVD and whether

healthy lifestyle/pharmacotherapies targeting inflammation can reduce CVD risk among multiparous women.

Clinical trial registration: The MESA cohort design is registered at clinicaltrials.gov as follows: https://clinicaltrials.gov/ct2/show/NCT00005487.

KEYWORDS

parity, inflammation, hsCRP, GlycA, fibrinogen, D-dimer, IL-6, pregnancy

Introduction

Cardiovascular disease (CVD) remains the leading cause of morbidity and mortality in the United States (U.S.) and worldwide (1, 2). CVD is responsible for one-third of the deaths in women worldwide, (1) and in the U.S. about 60 million women have prevalent CVD (1). Unfortunately, heart disease death rates are on the rise in younger and middle-aged women, (3, 4) emphasizing the importance of continued attention to strategies for preventing CVD in women (5, 6). Although there has been some progress including better understanding of some of the underlying pathophysiology of CVD in women, sex and gender disparities in cardiovascular health persist (7). These disparities exist in part due to the underrepresentation of women in previous research studies and the subsequent negative impact on prevention, diagnosis, and treatment for women at risk for CVD (7).

Beyond the traditional risk factors of CVD common in both men and women, evidence suggests that additional sex-based risk factors are important considerations for women (7, 8). These emerging non-traditional risk factors include pregnancy-related conditions such as gestational diabetes and hypertension, preeclampsia and eclampsia (9). Additionally, higher parity (number of live births) has also been shown to be associated with increased risk for future maternal CVD (10–13). A meta-analysis of 10 cohort studies found parity to be independently related to CVD risk with an association between higher number of pregnancies with greater risk of incident maternal CVD (13). Another study found that a history of grand multiparity ($\geq$5 live births) was associated with higher coronary heart disease risk, specifically myocardial infarction, even after adjusting for traditional risk factors (12). A history of grand multiparity has also been found to be associated with worse cardiovascular health (as assessed by the American Heart Association's Life Simple seven metrics) among middle-aged to older women (14). Additionally, when compared to nulliparous women, women with grand multiparity have a higher body mass index (BMI) later in life, (14) an adverse adipokine profile, (15) a more androgenic sex hormone profile, (16) and a greater burden of subclinical atherosclerosis, as assessed by the coronary artery calcium score (17).

The mechanisms linking parity to poorer cardiovascular health are not completely understood. However, the link between inflammation, as measured through several biomarkers, and risk of CVD has been well-documented (18–22). Thus, chronic inflammation may be one mechanism that explain the association between multiparity and increased CVD risk. However, the association of parity with inflammation has been inadequately explored to date.

Our study aims to evaluate the relationship between parity and several markers of inflammation and thrombosis, including high-sensitivity C-reactive protein (hsCRP), interleukin-6 (IL-6), GlycA, fibrinogen, and D-dimer, among middle-aged to older adult women using a multi-ethnic cohort. We hypothesized that increased parity will be associated with higher levels of inflammatory markers.

Materials and methods

Study population

The Multi-Ethnic Study of Atherosclerosis (MESA) consists of 6,814 women and men between the ages of 45 and 84 recruited from six study sites across the U.S., free from clinical CVD at the time of enrollment into the study. The study population at the baseline exam consisted of 38% White, 28% Black, 22% Hispanic, and 12% Chinese-American adults, of which 53% were women, all of whom were followed longitudinally to monitor for progression of subclinical CVD. Detailed descriptions of the study population and the conduct of the MESA study have been published elsewhere (23).

For our cross-sectional analysis at the baseline exam, we excluded all men ($n = 3,213$), women with missing parity status ($n = 2$), and those with missing baseline GlycA ($n = 18$), hsCRP ($n = 18$), IL-6 ($n = 68$), D-dimer ($n = 10$), and fibrinogen ($n = 4$) values. We also excluded participants missing observations for other key covariates ($n = 27$) except for pack-years of smoking and current use of menopausal hormone therapy to preserve sample size. Our final analytic sample included 3,454 participants (Supplementary Figure S1).

We obtained approval from Institutional Review Boards at each research center and informed consent from study participants prior to conducting the study.

Independent variables

Parity (number of live births) and gravidity (total number of pregnancies) were collected by self-report at baseline exam in 2000–2002 and defined based on prior research from the MESA cohort (14, 24). Parity was our primary independent variable for this analysis. Parity was modeled in categories: 0 (nulliparity, reference), 1–2, 3–4, or ≥5 live births, as has been done in previous analyses (14, 25, 26). In a supplemental analysis, we also examined gravidity and inflammation, using similar categories as parity.

Dependent variables

The dependent variables investigated in this study were the baseline measurements of GlycA, hsCRP, IL-6, D-dimer, and fibrinogen. At the baseline exam, serum levels of inflammatory markers, hsCRP, IL-6, fibrinogen, and D-dimer were measured, as previously reported (27–29). GlycA was measured using nuclear magnetic resonance spectra from EDTA plasma samples stored from the baseline visit. Detailed description on the ascertainment of GlycA measurements in MESA has also been previously described (21, 28, 29).

Covariates

We included demographic, behavioral, physiologic and CVD risk factors that were measured at the baseline exam from interview questionnaires, medication inventory, physical exam, and fasting laboratory work.

Age (years), BMI (kg/m^2), systolic blood pressure (mmHg), total cholesterol (mg/dl), and HDL-cholesterol (HDL-C) (mg/dl) were modeled continuously. Race/ethnicity (four groups), study site (six centers), education level (<high school; high school or vocational school; college, graduate, or professional school), smoking status (current/former/never), and menopause status (yes/no) were modeled as categorical variables. Pack-years of smoking and physical activity level (MET-min/week of moderate or vigorous activity) were modeled as continuous variables. Diabetes status (yes/no) was defined as fasting blood glucose ≥126 mg/dl, or non-fasting glucose ≥200 mg/dl or medication use (insulin or oral hypoglycemic medications). The use of lipid-lowering therapy, antihypertensive medications, and menopausal hormone therapy were considered binary variables (yes/no).

Statistical analyses

We examined baseline characteristics by parity categories. Continuous variables were presented as mean (SD). Categorical variables were presented as frequency (percentages). ANOVA and chi-square statistical tests were used to compare the differences between continuous and categorical variables, respectively.

The inflammatory markers were natural log-transformed in our statistical models to address the skewness of the data. We used progressively adjusted linear regression models to determine the cross-sectional association between parity categories and each of the five inflammatory markers separately. Model 1 adjusted for demographics (age, race/ethnicity) and study site. Model 2 (our primary analytical model) included covariates from model 1 and adjusted for lifestyle and physiologic factors including education, smoking status, pack-years of smoking, physical activity, BMI, menopause status, and current use of menopausal hormone therapy. For model 3, we included all covariates in model 2, plus CVD risk factors and medications, including total cholesterol, HDL-C, use of lipid-lowering medications, systolic blood pressure, use of antihypertensive medications and diabetes status.

The percent difference in the inflammatory markers for the parous groups compared to the reference parity category (i.e., no live births) was calculated from the regression models using the formula, $[\text{Exp}(\beta)-1] \times 100$.

In supplemental analyses, we examined for interactions of parity with obesity (BMI <30 vs. ≥30 kg/m^2) for the inflammatory markers using the likelihood ratio χ^2 test in model 2. Additionally, we repeated all models evaluating the association of gravidity (instead of parity) with the inflammatory markers.

Statistical significance was defined at a p-value <0.05. Analyses were performed using STATA Version 16.

Results

Baseline characteristics

Out of the 3,454 women included in our study sample, 18% were nulliparous women, 39% had 1–2 live births, 29% had 3–4 live births and 14% had 5 or more live births (Table 1). The overall mean age (SD) of our study population was 62 (10) years, and included 38% White, 28% Black, 22% Hispanic, and 12% Chinese-American women. Mean BMI was 29 (2) kg/m^2. Women with ≥5 live births were more likely to have higher systolic blood pressure, higher BMI, lower HDL-C, and more likely to have diabetes, as well as slightly higher prevalence of aspirin use (Table 1).

TABLE 1 Baseline characteristics of study participants by parity categories.

	Total	0	1–2	3–4	≥5	*p*-Value
	N = 3,454	*n* = 620	*n* = 1,357	*n* = 1,004	*n* = 473	
Age, years	62 (10)	60 (11)	60 (10)	63 (10)	68 (9)	<0.001
Race/ethnicity						
White	1,320 (38%)	311 (50%)	541 (40%)	362 (36%)	106 (22%)	<0.001
Chinese-American	412 (12%)	39 (6%)	177 (13%)	145 (14%)	51 (11%)	
Black	971 (28%)	191 (31%)	413 (30%)	248 (25%)	119 (25%)	
Hispanic	751 (22%)	79 (13%)	226 (17%)	249 (25%)	197 (42%)	
Education						
≥ bachelor's degree	1,029 (30%)	315 (51%)	451 (33%)	235 (23%)	28 (6%)	<0.001
<bachelor's degree	2,425 (70%)	305 (49%)	906 (67%)	769 (77%)	445 (94%)	
Smoking status						
Never	2,040 (59%)	328 (53%)	754 (56%)	641 (64%)	317 (67%)	<0.001
Former	1,013 (29%)	214 (35%)	425 (31%)	267 (27%)	107 (23%)	
Current	401 (12%)	78 (13%)	178 (13%)	96 (10%)	49 (10%)	
*Pack-years of smoking, if >0	14 (5, 29)	15 (7, 29)	14 (5, 28)	14 (6, 32)	11 (5, 31)	0.66
Physical activity, MET-min/weeks	3,720 (1,832, 6,810)	3,949 (2,010, 6,319)	3,720 (1,875, 6,878)	3,893 (1,983, 7,241)	2,745 (1,118, 6,090)	<0.001
BMI, kg/m^2	29 (6)	28 (6)	28 (6)	29 (6)	30 (6)	<0.001
Menopause						
Yes	2,961 (86%)	491 (79%)	1,124 (83%)	895 (89%)	451 (95%)	<0.001
No	493 (14%)	129 (21%)	233 (17%)	109 (11%)	22 (5%)	
Hormone therapy†						
Yes	986 (32%)	179 (33%)	415 (35%)	298 (32%)	94 (21%)	<0.001
No	2,129 (68%)	357 (67%)	786 (65%)	631 (68%)	355 (79%)	
Systolic blood pressure, mmHg	127 (23)	124 (23)	125 (23)	128 (23)	134 (24)	<0.001
Total cholesterol, mg/dl	200 (36)	200 (34)	200 (36)	199 (35)	199 (37)	0.99
HDL-C, mg/dl	56 (15)	59 (16)	57 (15)	55 (15)	53 (13)	<0.001
Diabetes	389 (11%)	46 (7%)	146 (11%)	118 (12%)	79 (17%)	<0.001
Antihypertensive medication	1,308 (38%)	196 (32%)	498 (37%)	400 (40%)	214 (45%)	<0.001
Lipid-lowering medication	565 (16%)	82 (13%)	231 (17%)	172 (17%)	80 (17%)	0.14
NSAIDS excluding Aspirin	740 (21%)	143 (23%)	308 (23%)	194 (19%)	95 (20%)	0.14
Aspirin‡	550 (17%)	95 (16%)	187 (14%)	178 (18%)	90 (20%)	0.02
GlycA, umol/L	390 (351, 435)	383 (344, 424)	393 (351, 439)	391 (352, 436)	390 (355, 434)	<0.01
CRP, mg/L	2.5 (1.0, 5.6)	2.1 (0.9, 4.5)	2.6 (1.0, 6.0)	2.6 (1.1, 5.6)	3.0 (1.3, 5.9)	<0.001
IL-6, pg/ml	1.3 (0.8, 1.9)	1.2 (0.8, 1.8)	1.2 (0.8, 1.9)	1.3 (0.9, 1.9)	1.6 (1.0, 2.3)	<0.001
Fibrinogen, mg/dl	352 (308, 403)	347 (305, 402)	346 (300, 398)	358 (313, 406)	368 (327, 412)	<0.001
D-dimer, μg/ml	0.2 (0.2, 0.4)	0.2 (0.1, 0.4)	0.2 (0.1, 0.4)	0.3 (0.2, 0.4)	0.3 (0.2, 0.6)	<0.001

BMI, body mass index; CRP, c-reactive protein; HDL-C, high-density lipoprotein-cholesterol; IL-6, interleukin-6; MET, metabolic equivalent of task; NSAIDS, non-steroidal anti-inflammatory drugs.
Data were presented as mean (SD), median (IQR) or number (percentage).
*N = 3,422 for pack-years of smoking; †N = 3,115 for hormone therapy; ‡N = 3,300 for Aspirin.

Inflammatory markers

The association between parity categories and log-transformed inflammatory markers are displayed in Table 2.

For GlycA, a history of 1–2 live births was associated with higher levels of GlycA across all three adjusted models, compared to nulliparity. However, for women with 3–4 live births, a significant difference for higher GlycA was observed only after adjustment for demographic factors (model 1) and was attenuated after further adjustment. There was no statically significant difference for grand-multiparity (i.e., ≥5 live births) with GlycA when compared to the reference in any of the three models.

TABLE 2 Association between parity and inflammatory markers in MESA.

Parity	*N*	Model 1, *N* = 3,454	Model 2, *N* = 3,087	Model 3, *N* = 3,087
		Percent difference (95% CI)		
GlycA				
0	620	Reference	Reference	Reference
1–2	1,357	**3 (1, 4)**	**2 (1, 4)**	**2 (1, 4)**
3–4	1,004	**2 (1, 4)**	1 (0, 3)	1 (0, 3)
≥5	473	1 (−1, 3)	−1 (−3, 1)	−1 (−3, 1)
CRP				
0	620	Reference	Reference	Reference
1–2	1,357	**25 (12, 39)**	**18 (6, 30)**	**18 (7, 31)**
3–4	1,004	**27 (13, 43)**	**17 (4, 30)**	**16 (4, 30)**
≥5	473	**28 (11, 48)**	12 (−2, 29)	12 (−3, 28)
IL-6				
0	620	Reference	Reference	Reference
1–2	1,357	−4 (−9, 2)	−3 (−8, 3)	−2 (−8, 3)
3–4	1,004	2 (−5, 8)	1 (−5, 7)	0 (−6, 7)
≥5	473	**10 (1, 19)**	1 (−7, 9)	0 (−7, 8)
Fibrinogen				
0	620	Reference	Reference	Reference
1–2	1,357	−1 (−2, 1)	−1 (−3, 1)	−1 (−3, 1)
3–4	1,004	1 (−1, 3)	0 (−2, 3)	0 (−2, 2)
≥5	473	0 (−2, 3)	−2 (−4, 1)	−2 (−4, 1)
D-dimer				
0	620	Reference	Reference	Reference
1–2	1,357	1 (−6, 10)	1 (−7, 10)	1 (−7, 10)
3–4	1,004	7 (−2, 17)	5 (−4, 15)	5 (−4, 15)
≥5	473	**18 (6, 31)**	10 (−2, 23)	10 (−2, 23)

CRP, c-reactive protein; IL-6, interleukin-6; MESA, multi-ethnic study of atherosclerosis.
Results were presented as percent difference calculated from [exp (β)−1] × 100 for the association between parity and natural log-transformed inflammatory markers.
Reference = 0 (nulliparous).
Statistical significant results at $p < 0.05$ are in bold font.
Model 1 (demographics and study site): age, race/ethnicity and study site.
Model 2 (model 1 + lifestyle and physiologic factors): education, smoking status, pack-years of smoking, physical activity, BMI, menopause status and current use of menopausal hormone therapy.
Model 3 (model 2 + CVD risk factors and medications): total cholesterol, HDL-C, lipid-lowering medication, systolic blood pressure, antihypertensive medication and diabetes.

For hsCRP, women with a history of 1–2 live births and 3–4 live births had higher levels compared to nulliparous women in all three adjusted models. After full adjustment for all CVD risk factors (model 3), women with 1–2 live births and 3–4 live births had 18 and 16% higher hsCRP levels, respectively, compared to nulliparous women. Women with ≥5 live births had higher hsCRP levels in the demographic adjusted model (model 1) only.

For IL-6 and D-dimer, women with a history ≥5 live births were found to have higher levels in the unadjusted (Figure 1) and demographic adjusted models (model 1) only. There was no significant association of parity with fibrinogen.

In a supplemental analysis, we found no statistically significant interaction of parity with BMI on any of the inflammatory markers ($p > 0.05$).

Additional supplemental analysis for gravidity (Supplementary Table S1) showed that out of the 3,454 women included in our study sample, 13% were nulligravida women, 32% had 1–2 pregnancies, 33% had 3–4 pregnancies and 23% had 5 or more pregnancies. Multigravida women were more likely to be Hispanic, have higher systolic blood pressure, higher BMI, lower HDL-C and more likely to have diabetes (Supplementary Table S1).

The association between gravidity categories and log-transformed inflammatory markers are displayed in Supplementary Table S2. For GlycA, a history of 1–2 pregnancies was associated with higher levels of GlycA for model 1 alone, compared to nulligravida.

For hsCRP, women with a history of 1–2 pregnancies and 3–4 pregnancies had higher levels compared to nulligravida

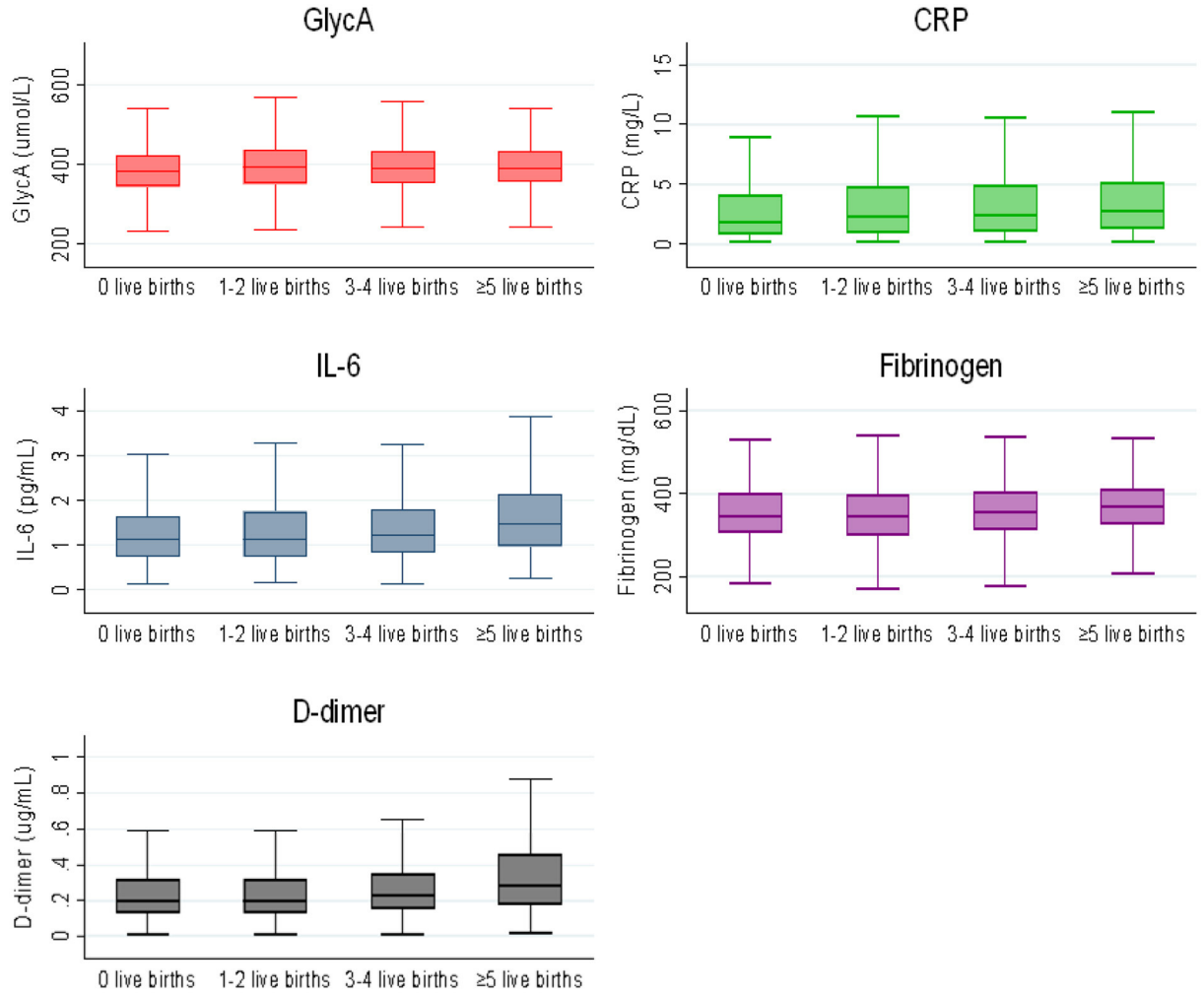

FIGURE 1
Box plot of inflammatory markers by parity categories. The lower and upper boundaries of the rectangles denote the 25th and 75th percentiles while the horizontal line within the rectangles is the median. Lines extend from the rectangles to the smallest and largest values within 1.5× interquartile range.

women in all three adjusted models. After adjustment for all CVD risk factors (model 3), women with 1–2 pregnancies and 3–4 live births had 21 and 18% higher hsCRP levels, respectively, compared to women who had no pregnancy history. Women with a history of ≥5 pregnancies were found to have 25% higher hsCRP and 11% higher D-dimer levels in the demographic adjusted model (model 1) only compared to nulligravida women, which was no longer statistically significant after further covariate adjustment. There were no significant associations between gravidity and IL-6 or fibrinogen across all models and gravidity categories, compared to the nulligravida group.

Discussion

In this multi-ethnic cohort of women who were free of CVD at initial time of assessment, we found that a history of higher parity was positively associated with some inflammatory markers, though these finding did not always remain statistically significant with in fully adjusted models. Specifically, we found that after accounting for differences in age, race/ethnicity, lifestyle and physiologic factors, as well as CVD risk factors and medication use, women with a history of 1–2 live births were found to have higher levels of GlycA and hsCRP compared to nulliparous women. Women with a history of 3–4 live births also had higher hsCRP levels compared to women with no live births. Women with grand multiparity (≥5 live births) had higher levels of hsCRP, IL-6, and D-dimer in demographic adjusted models, but this was attenuated and no longer statistically significant after adjustment for CVD risk factors. Thus, there was no clear dose-response relationship between parity and inflammatory levels.

Nevertheless, we did find that the associations of parity and inflammation were strongest for hsCRP. Our findings

are comparable with another prior cross-sectional study of Mexican-American women, which also found parity to be associated with elevated CRP (30). Another cross-sectional analysis showed that the inflammatory marker, IL-12, was elevated in those increasing parity (categorized as 0, 1, 2, 3, and 4 or more pregnancies), although the relationship was not significant after adjusting for smoking (31). These studies, plus our findings, suggest that parity may be more closely related to certain inflammatory markers.

Women tend to gain weight on average with each subsequent pregnancy, and prior work in MESA confirmed that women with grand multiparity had higher BMIs compared to other parous groups (14). Adipokines (hormones secreted by adipose tissue) play a role in both normal and abnormal pregnancies, (32) and adipokine dysregulation may be one mechanism by which pregnancy-associated weight changes may confer later life maternal CVD risk (15). It is well-established that adiposity leads to a pro-inflammatory state (33). Although we hypothesized that greater parity would be independently associated with inflammatory markers, perhaps it is not surprising that indeed for several inflammatory markers (i.e., IL-6 and D-dimer), associations between grand multiparity were attenuated and no longer significant after accounting for BMI in model 2. However, parity did remain associated with hsCRP even in fully adjusted models, including BMI, at least for 1–2 and 3–4 live births. Our analysis did not reveal an influence of BMI on the association between parity and inflammation. In prior studies, higher BMI has been associated with chronic inflammation and adipose tissue has been shown to release pro-inflammatory cytokines (34, 35). Thus, the association between parity and inflammation may be mediated by another factor not evaluated in our study.

We found similar findings for gravidity, with the strongest association observed with hsCRP. The discrepancies in association using gravidity in comparison to parity, lies in the confounder that women with higher gravidity may or may not have been successful in completing their pregnancy for several reason, which may confer different risk for CVD.

Strengths and limitations

Our study was meant to be exploratory to determine if there was a link between parity history and later life inflammatory risk in women. However, our study findings should be considered in the context of several limitations. First, it is an observational study; therefore, causality cannot be inferred; residual confounding may explain some of the associations seen. Additionally, with a cross-sectional analysis, it is prone to temporal and survival bias. Women in our study had a mean age of 62 and were predominantly menopausal; thus, the inflammatory markers were measured on average a significant number of years from the women's last pregnancies, and unfortunately, we did not have the age at last pregnancy available to determine the time lag. Using the average menopause age for U.S. women, of 51 years, there are at least 11 years on average from last pregnancy at the time of the study. Third, we may also have adjusted for some mediators between parity and inflammation such as BMI that led to attenuation of the relationship between parity and inflammation. Fourth, there was a smaller sample size for the grand multiparous group, which may have contributed to less statistical power to detect a significant difference. Additionally, a key confounder in multiparity is social class, which was adjusted for by considering two categories of education and may result in residual confounding. Finally, there was no information collected in MESA about adverse pregnancy outcomes such as pre-eclampsia, gestational diabetes or preterm birth, so we could not examine a history of these high-risk pregnancy conditions with later life inflammatory markers.

The strengths of our study include the use of a multi-ethnic cohort of women who were free of CVD at baseline. We adjusted for numerous confounders in our models for the relationship between parity and inflammation. This study contributes to the currently under-explored area in understanding the potential mechanism in which higher parity may be contributing to poorer cardiovascular outcomes in women. To our knowledge, our study was the first to explore the association of parity with later life elevations of other markers of inflammation and thrombosis (i.e., GlycA, IL-6, fibrinogen, and D-dimer).

Conclusion

In this diverse cohort of mid-life to older-aged women free from clinical CVD, we found a history of higher parity was positively associated with some inflammatory markers; however, these associations were largely attenuated after adjustment for lifestyle and CVD risk factors. There was no clear dose-response relationship between higher parity status and higher inflammatory levels. Future studies are needed to evaluate how other markers of inflammation may influence the link between parity and CVD and whether lifestyle/pharmacotherapy targeting inflammation can reduce CVD risk among multiparous women.

Data availability statement

The datasets presented in this article are not readily available but datasets can be made available by request to the MESA Publications Committee after signing Data Transfer Agreement or by submitting a request to NIH

NHBLI BioLincc at https://biolincc.nhlbi.nih.gov/studies/mesa//. Requests to access the datasets should be directed to https://biolincc.nhlbi.nih.gov/studies/mesa/.

Ethics statement

The studies involving human participants were reviewed and approved by Johns Hopkins University Institutional Review Board. The patients/participants provided their written informed consent to participate in this study.

Author contributions

AE and EM designed the study. AE performed statistical analysis under supervision of OOg. AE wrote the first draft under EM mentorship. AM, OOs, OF, CR, BK, LK, and CH provided critical scientific input to manuscript draft. All authors approved of the final submission.

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Conflict of interest

Unrelated to this work, Author EM has served on advisory boards for Pfizer, Esperion, Novartis, Novo Nordisk, Bayer, Boehringer Ingelheim, Amarin, and Astra Zeneca.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.922367/full#supplementary-material

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Wave separation analysis-derived indexes obtained from radial and carotid tonometry in healthy pregnancy and pregnancy-associated hypertension: Comparison with pulse wave analysis-derived indexes

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Background: Increased wave reflections assessed by pulse wave analysis (PWA) was proposed as one of the potential culprits of hypertension seen in women with pregnancy-associated hypertension (PAH). However, this statement has never been confirmed with "Wave Separation Analysis" (WSA), a more sophisticated mathematical approach that analyzes the amplitude and interaction between forward and backward aortic pressure waveform components.

Objective: To characterize potential changes in pressure wave components of PAH compared to healthy non-pregnant (NP) women and women with normal pregnancies (HP) by using WSA and compared these findings with PWA-derived indexes; secondarily, to evaluate differences in WSA-derived indexes between subgroups of PAH (i.e., preeclampsia [PE] and gestational hypertension [GH]).

Methods: Using radial and carotid applanation tonometry, we quantified in HP (n = 10), PAH (n = 16), and NP (n = 401): (i) PWA-derived indexes; (ii) WSA-derived indexes: forward (Pf) and backward (Pb) waveform components, backward component arrival time (PbAT), reflection magnitude (RM = Pb/Pf) and index [RIx = Pb/(Pf + Pb)].

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Results: While PAH was associated with a higher Pf compared to HP and NP, Pb and PbAT were similar between the groups. Both GH and PE showed a higher Pf compared to HP, but only PE had a trend of presenting with higher Pb and lower PbAT compared to the other groups. Finally, PAH showed a trend of having lower RM and RIx compared to NP and HP, with no differences between GH and PE.

Conclusion: PAH was associated with higher Pf, but not higher Pb, compared to NP and HP, although PE also demonstrated a trend of higher Pb.

KEYWORDS

applanation tonometry, gestational hypertension, pregnancy, preeclampsia, pulse wave analysis, wave separation analysis

Introduction

Healthy pregnancy (HP) is characterized by a myriad of changes in the structure and function of the maternal cardiovascular system that are evident early during pregnancy (1, 2). These modifications, including an enhancement of endothelial function, a drop in the peripheral vascular resistance and aortic stiffness, and the preservation of the stiffness gradient (3) are all critical to ensure a sufficient utero-placental perfusion (to meet the fetal metabolic demands) with no increments in the blood pressure (2–4).

Recent evidence supports the "cardiovascular maladaptation hypothesis" of preeclampsia (PE]), in which the inability of the great arteries to adapt properly (arterial impairment) imposes additional hemodynamic loads on the maternal and fetal circulations leading to further hemodynamic derangements (3, 5). In this context, the possibility of measuring the level or degree of cardiovascular maladaptation to pregnancy that can occur in different pregnancy-associated hypertension (PAH) disorders not only would allow for a comprehensive understanding of their pathophysiology but can also be an opportunity to generate new preventive diagnostic tools and treatments (6–8). Among different tools, the examination of central pressure waveform-derived indexes, using "pressure-only approaches for waveform analysis," has been promising (9–15).

The most widely used model to analyze the central pressure waveform is based on the "Pulse Wave Analysis" (PWA) approach, which allows for the quantification of augmentation pressure (AP) and augmentation index (AIx), along with their heart rate (HR) corrected versions (APHR75, AIxHR75, respectively), and subendocardial viability ratio (SEVR) (15, 16) (**Figure 1**). The theoretical concept underlying PWA is that forward waves generated by the left ventricle (LV) travel to the periphery, reflect distally, and travel back fast enough to collide with forward pressure (Pf) waves, thereby augmenting the (central) aortic systolic and pulse pressures (aoSBP, aoPP, respectively). Several groups quantified PWA-derived indexes in pregnant women in order to characterize potential specific pregnancy-induced physiological variations and differences between HP and PAH states, including PE (6, 8, 17–19). While some investigators found that PAH states (in particular PE) are associated with a higher AIx (or AIxHR75) in comparison to HP (17, 18), others found no differences in these indexes among these pregnant women (8, 20, 21). Several biological and/or methodological reasons may explain this controversy.

More recently, other "pressure-only approaches" for waveform analysis, such as "Wave Separation Analysis" (WSA), have been introduced. In this approach, the central pressure waveform, which integrates different forward and backward propagating waves, is decomposed into single forward (Pf) and backward (Pb) components (**Figure 1**). Several clinical studies have shown that WSA could provide valuable clinical information about hemodynamics and cardiovascular efficiency (13, 15, 22). However, to the best of our knowledge, it remains unknown whether WSA-derived indexes change in pregnancy, particularly, in women with PAH. As PWA and WSA-derived indexes are influenced by common variables (e.g., arterial

Abbreviations: Aix, augmentation index; AIxHR75, AIx corrected for heart rate equal 75 beats/minute; aoBP, central aortic blood pressure; aoPP, aortic pulse pressure; aoSBP, aortic systolic blood pressure; AP, augmentation pressure; APHR75, AP corrected for heart rate equal 75 beats/minute; baBP, brachial artery blood pressure; baDBP, brachial artery diastolic blood pressure; baMBP, brachial artery mean blood pressure; baSBP, brachial artery systolic blood pressure; BH, body height; BMI, body mass index; BW, body weight; CRFs, cardiovascular risk factors; CT, carotid artery applanation tonometry; CVD, cardiovascular disease; DTTI, diastolic pressure or tension-time area or index; GH, gestational hypertension; GTF, general transfer function; HP, healthy pregnancy; HR, heart rate; NP, non-pregnant; PA, physical activity; PAH, pregnancy-associated hypertension; Pb, amplitude of central backward blood pressure component; Pb AT, central backward pressure arrival time to central pressure waveform; PE, preeclampsia; Pf, amplitude of central forward blood pressure component; PWA, pulse wave analysis; RIx, reflection index; RM, reflection magnitude; RT, radial artery applanation tonometry; SEVR, subendocardial viability ratio; STTI, systolic pressure or tension-time area or index; WSA, wave separation analysis.

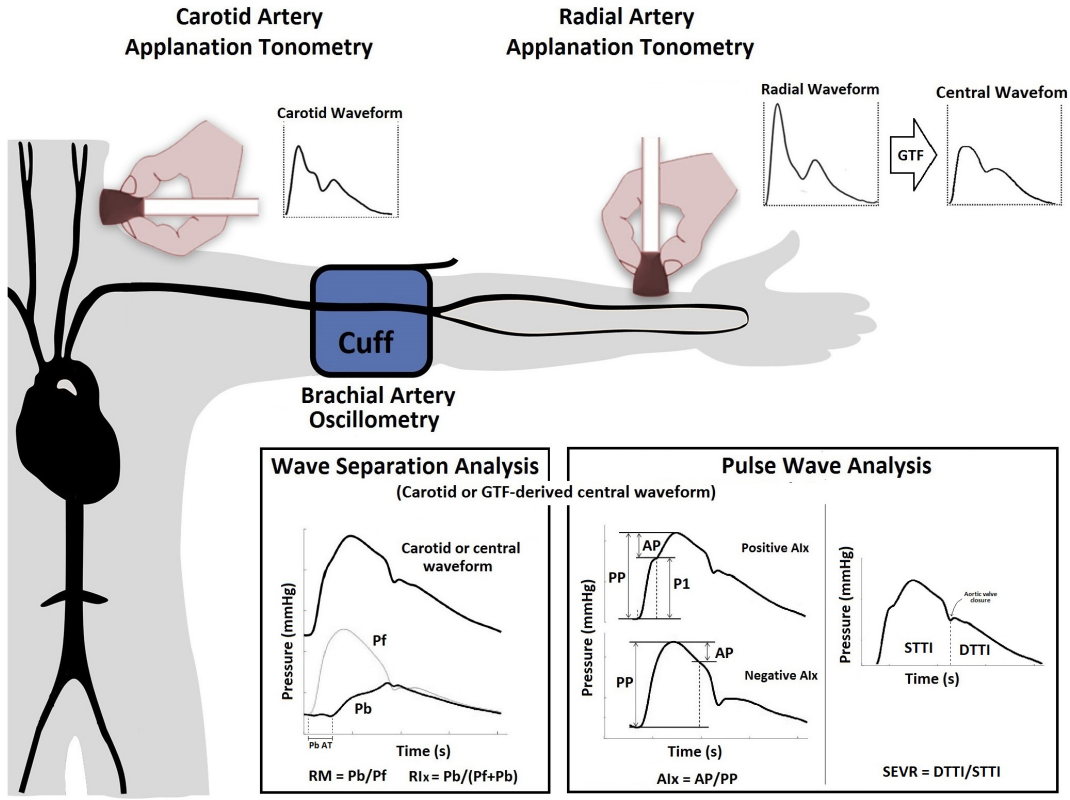

FIGURE 1
Use of applanation tonometry (radial or carotid) for the assessment of PWA and WSA. PWA: The AP represents the direct augmentation level caused by wave reflections (a positive AP indicates "additional" pressure arising from wave reflections) (36), and is calculated from the inflection point in the pressure waveform (systolic phase) that "points out or identifies" the arrival of the reflected component to the aortic root (37). AIx (either a positive or negative value) is calculated as AP/aoPP and is considered a surrogate index of wave reflection, although it also depends on factors like HR, vascular tone, or LV function (22). SEVR, quantified as the ratio between aortic diastolic and systolic tension-time areas or indexes [STTI and DTTI], represents a parameter of myocardial oxygen supply and demand that can be altered by changes in diastolic and systolic pressures as a result of changes in the arrival of the backward pulse wave (16). WSA: The Pf represents the integration of the forward wave arising from the ventricle and re-reflections of backward propagating waves at the ventricular-aorta interface. Using Pf and Pb, the reflection magnitude (RM = Pb/Pf) and index [RIx = (Pb/(Pf + Pb)] can be obtained (13, 38). Abbreviations as in text.

stiffness), the variables derived by these approaches could show association between one another. Nevertheless, the information provided by WSA-derived indexes could differ, complement, or even offer better information during normal pregnancy or pregnancy complicated by PAH than PWA-derived indexes. Besides, the WSA-derived indexes could be useful for the identification of variations associated with PAH states. Finally, it is noteworthy that several techniques (e.g., applanation tonometry, plethysmography) and mathematical methods [e.g., direct carotid or distal-arteries recordings associated to a general transfer function (GTF)] have been proposed to perform PWA and WSA (22, 23). Our group has previously worked in this area, demonstrating that values of a single WSA- or PWA-derived index (e.g., AIx, Pf) could markedly differ based on the technique and recording site (e.g., carotid [CT] vs. radial [RT] applanation tonometry) (23, 24).

In this context, we sought to analyze (1) the levels of association between WSA and PWA derived indexes and (2) to characterize and compare WSA-derived indexes in HP and PAH. Additionally, we identified potential differences between subgroups of PAH patients (i.e., PE and GH). Considering the different approaches to obtaining these non-invasive indexes, we employed the gold-standard technique (i.e., applanation tonometry) with two different ways of recording: RT (indirect method that requires a GTF) and CT (direct method that does not require a GTF).

Materials and methods

Subjects

This was a cross-sectional study involving NP, and pregnant women from our CUiiDARTE Project database (25–28). Cardiovascular evaluation in the CUiiDARTE Project involves a stepwise protocol using several equipment and devices that

measure structural and functional properties of central and peripheral arteries, as well as hemodynamic variables (25–28). All procedures were conducted in agreement with the Declaration of Helsinki and approved by the Institution's Ethics Committee. Written informed consent was obtained prior to the examination. The data presented in this work was obtained in a study protocol, which has already given rise to a recent publication related to other aspects of arterial behavior in normal and pathophysiological circumstances (7). Healthy NP (n = 401) women were selected to be matched for age and global cardiovascular risk factors (CRFs) with the below-mentioned pregnant women. By using propensity score matching methods, an efficient matching and balance is created among the mentioned covariates, thereby, minimizing or entirely removing their confounding effect (29). HP women (n = 10), without known family history of premature cardiovascular disease (CVD), were recruited from the routine antenatal clinic. All women had uncomplicated pregnancies before and during the study. Women with PAH (n = 16) were recruited from the antenatal hospital ward, where they were admitted due to mild hypertension (brachial artery blood pressure [baBP] 140/90 to 149/109 mmHg).

According to the Bulletin of the American College of Obstetricians and Gynecologists (30), PAH is defined as baSBP of 140 mm Hg or more or baDBP of 90 mm Hg or more on two occasions at least 4 h apart after 20 weeks of gestation in a woman with a previously normal BP. Depending on whether there was significant proteinuria (≥300 mg per 24-h urine collection), patients were further classified as PE or GH, respectively, since all patients included in the study had no evidence of severe features. Laboratory samples were obtained prior to the study enrollment. A clinical interview, together with the anthropometric evaluation (body weight [BW], height [BH] and mass index [BMI]) enabled us to assess for CRF exposure (i.e., family history of CVD, obesity, dyslipidemia).

Non-invasive arterial evaluation: Central blood pressure levels and wave separation analysis- and pulse wave analysis-derived indexes

Central aortic blood pressure (aoBP) levels and waveforms were obtained (random order) using a commercially available device: SphygmoCor-CvMS (v.9, AtCor-Medical, Sydney, NSW, Australia). Subjects were instructed to lie in a left lateral position (to avoid vena cava compression by the uterus) in a temperature-controlled (21–23°C) room, for at least 15 min, in order to establish stable hemodynamic conditions. The aoBP waveforms were derived from, (i) radial artery (applying a GTF) and (ii) carotid artery (directly) manual tonometric recordings (**Figure 1**). Carotid pulse waveforms were assumed to be identical to the aortic ones (due to the proximity of the arterial sites) (31). Thus, a GTF was not applied to obtain central waveforms from carotid recordings. Only accurate waveforms on visual inspection and high-quality recordings (in-device quality control [operator] index > 95%) were considered.

The SphygmoCor device was used for WSA and PWA. A detailed explanation of the method used for waveform analysis based on recorded carotid waveforms and mathematically-derived aortic waveforms was included as **Supplementary material** in a previous study (24). As was previously published, the absolute and relative intra- (repeatability) and interobserver (reproducibility) variability of aoBP levels and waveform-derived indexes was analyzed considering different methodological approaches (RT and CT) (23, 24). In all cases, relative inter- and intraobserver variability was < 6%.

Using applanation tonometry and two recording sites (carotid and radial), we quantified: (i) PWA-derived indexes: AP, APHR75, AIx, AIxHR75, STTI, DTTI, SEVR, and (ii) WSA-derived indexes: Pf, Pb, Pb AT (backward pressure arrival time to central pressure waveform), RM, and RIx (**Figure 1** and **Supplementary Table 1**). Recorded waveforms were calibrated using brachial artery diastolic (baDBP) and mean blood pressures [baMBP = baDBP + (baSBP-baDBP)/3], where baSBP is brachial artery systolic blood pressure (23, 24).

Data analysis

First, after descriptive statistics were computed (**Table 1** and **Supplementary Table 2**), aimed at determining whether the WSA-derived indexes are related to PWA-derived indexes, we analyzed the level of association between them by assessing simple bivariate correlation (Pearson coefficients, r) (**Table 2**). Second, one-way analysis of covariance (ANCOVA) with multiple adjusted comparisons was used for the evaluation of differences in cardiovascular variables. Demographic characteristics (age), anthropometric measurements (BW, BH, BMI), CRFs exposure and medication use were categorized as adjustment variables. Considering the relatively small sample sizes of the HP and PAH groups, we performed bootstrapping of the samples (both, for correlations and ANCOVA) as a strategy to evaluate whether potential statistical differences observed between the study groups are maintained even after analyzing different random sampling settings. To this end, bootstrap-derived 95% confidence intervals (1,000 samples) were obtained applying bias-corrected and accelerated methods for computing confidence interval limits (32). In other words, with this statistical mechanism, any initial $p < 0.05$ may no longer be significant after the "fictional random re-sampling" (i.e., bootstrapping). This type of test is a conservative approach that obligates the investigators to consider only those significant p-values that replicate in both statistical scenarios (i.e., the actual sample and bootstrapping sampling). As secondary

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TABLE 1 Clinical and blood pressure levels and waveform-derived indexes according to the study groups.

	Non-pregnant women				Healthy pregnant women				Pregnancy-associated hypertension			
	MV	*SE*	Min.	Max.	MV	*SE*	Min.	Max.	MV	*SE*	Min.	Max.
Age [years]	22.84	0.30	18	41	29.40	1.95	21.00	40	32.25	1.56	20.00	40.00
BMI [Kg/m^2]	23.04	0.22	16.50	48.77	27.13	1.13	20.72	31.23	34.16	1.78	21.77	48.27
Hypertension [%]	4.0%				0.0%				100.0%			
BP treatment (%)	1.7%				0.0%				12.5%			
Dyslipidemia (%)	7.2%				20.0%				0.0%			
Basic hemodynamics												
baSBP [mmHg]	118	1	85	177	114	2	106	121	127	3	98	143
baDBP [mmHg]	69		49	103	65	3	52	85	75	2	59	93
HR [bpm]	69	1	43	102	77	8	51	93	82	3	69	95
Radial applanation tonometry												
aoSBP [mmHg]	103	1	79	156	99	2	90	110	112	3	84	126
aoDBP [mmHg]	70		47	103	67	3	55	87	78	2	60	94
aoPP [mmHg]	33		17	68	33	2	22	46	33	2	24	44
AP [mmHg]	2		−13	18	3	1	−2	6	4	1	−3	13
AIx	7	1	−26	41	9	3	−6	18	12	3	−11	31
SEVR	144	1	77	261	128	11	86	183	123	7	87	177
Pf [mmHg]	30		15	68	28	3	16	42	29	1	22	39
Pb [mmHg]	14		5	39	14	1	8	22	13	1	9	20
Pb AT [ms]	252	1	180	477	240	8	203	281	244	5	211	281
RM	0.48	0.01	0.17	1.00	0.53	0.04	0.38	0.77	0.45	0.02	0.31	0.65
RIx	0.32	0.00	0.14	0.50	0.34	0.02	0.27	0.44	0.31	0.01	0.24	0.39
Carotid applanation tonometry												
aoSBP [mmHg]	110	1	73	164	112	7	96	146	117	5	81	147
aoDBP [mmHg]	66	1	48	100	69	5	53	85	72	3	54	95
aoPP [mmHg]	44	1	10	80	43	9	21	84	45	4	27	85
AP [mmHg]	−6	1	−32	32	−8	6	−33	4	−4	4	−50	14
AIx	−12	1	−47	40	−12	9	−39	10	−5	7	−58	34
SEVR	145	2	93	223	130	19	70	187	121	4	86	151
Pf [mmHg]	44	1	8	107	34	5	19	46	45	5	24	85
Pb [mmHg]	16		6	31	16	3	11	26	17	2	9	28
Pb AT [ms]	270	3	211	445	262	14	219	289	258	13	211	375
RM	0.41	0.01	0.15	0.96	0.50	0.07	0.24	0.63	0.43	0.05	0.15	0.70
RIx	0.28	0.00	0.13	0.49	0.32	0.04	0.19	0.39	0.29	0.03	0.13	0.41

MV, mean value; SE, standard error; Min, minimal value; Max, maximal value; BMI, body mass index; SBP, PP, DBP, MBP, systolic pulse, diastolic and mean blood pressure; ao, aortic; ba, brachial artery; ra, radial artery; BP, blood pressure; Pf, central forward pulse pressure height; Pb, central backward pulse pressure height; PbAT, central backward arrival time; AIx, augmentation index; AP, central augmented pressure; SEVR, sub-endocardial viability ratio; HR, heart rate; RM, reflection magnitude; RIx, reflection index. Sample size: non-pregnant women (n = 401), healthy pregnant (n = 10), pregnancy-associated hypertension (n = 16).

analysis, we further investigate differences between four groups (NP, HP, GH, PE) by discriminating between women with PE and GH within the PAH group.

Normality of the distribution of the data was examined using the Shapiro–Wilk test and Q-Q plots, with $P < 0.05$ indicating significant statistical differences. The statistical analyses were performed using the Statistical Package for Social Sciences (version 26.0). Evans's Empirical Classification ("correlation strength") was used for r interpretation as follows: <0.20, very weak; 0.20–0.39, weak; 0.40–0.59, moderate; 0.60–0.79, strong; ≥0.80, very strong (33).

Results

Descriptive characteristics and baseline cardiovascular parameters of the study groups are presented in Table 1 and Supplementary Table 1. The mean gestational age at examination of all the pregnant women was 35 ± 3 weeks.

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TABLE 2 Association between hemodynamic and waveform derived indexes.

		Radial applanation tonometry					Carotid applanation tonometry				
		Pf (mmHg)	Pb (mmHg)	Pb AT (ms)	RM	RIx	Pf (mmHg)	Pb (mmHg)	Pb AT (ms)	RM	RIx
Radial applanation tonometry											
baSBP (mmHg)	*r*	0.786	0.545	0.046	−0.353	−0.367	0.507	0.291	0.075	−0.261	−0.252
	p	<0.001	<0.001	0.193	<0.001	<0.001	<0.001	<0.001	0.172	<0.001	0.001
baDBP (mmHg)	*r*	−0.439	−0.126	−0.304	0.345	0.367	−0.276	−0.066	−0.361	0.257	0.256
	p	<0.001	0.009	<0.001	<0.001	<0.001	<0.001	0.201	<0.001	<0.001	<0.001
baMBP (mmHg)	*r*	−0.156	0.129	−0.284	0.266	0.282	−0.020	0.123	−0.327	0.164	0.160
	p	0.002	0.008	<0.001	<0.001	<0.001	0.401	0.059	<0.001	0.019	0.021
aoSBP (mmHg)	*r*	0.372	0.536	−0.088	0.101	0.093	0.343	0.352	−0.099	−0.010	−0.014
	p	<0.001	<0.001	0.048	0.028	0.041	<0.001	<0.001	0.107	0.450	0.428
aoDBP (mmHg)	*r*	−0.439	−0.135	−0.321	0.334	0.356	−0.261	−0.079	−0.360	0.231	0.229
	p	<0.001	0.005	<0.001	<0.001	<0.001	<0.001	0.160	<0.001	0.002	0.002
AP (mmHg)	*r*	−0.504	0.282	−0.195	0.820	0.819	−0.341	0.112	−0.253	0.476	0.443
	p	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.078	0.001	<0.001	<0.001
AIx (%)	*r*	−0.570	0.194	−0.168	0.858	0.861	−0.341	0.109	−0.210	0.501	0.467
	p	<0.001	<0.001	0.001	<0.001	<0.001	<0.001	0.084	0.004	<0.001	<0.001
SEVR	*r*	0.012	0.279	0.203	0.290	0.297	0.078	0.346	0.161	0.251	0.261
	p	0.407	<0.001	<0.001	<0.001	<0.001	0.161	<0.001	0.020	0.001	<0.001
Pf(mmHg)	*r*	1	0.546	0.296	−0.577	−0.602	0.554	0.323	0.221	−0.316	−0.301
	p	——-	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.003	<0.001	<0.001
Pb (mmHg)	*r*	0.546	1	0.024	0.320	0.307	0.318	0.473	0.120	0.127	0.105
	p	<0.001	——-	0.329	<0.001	<0.001	<0.001	<0.001	0.066	0.056	0.094
Pb AT (ms)	*r*	0.296	0.024	1	−0.239	−0.264	0.030	0.183	0.300	0.076	0.093
	p	<0.001	0.329	——-	<0.001	<0.001	0.353	0.011	<0.001	0.171	0.121
RM	*r*	−0.577	0.320	−0.239	1	0.991	−0.358	0.072	−0.128	0.527	0.481
	p	<0.001	<0.001	<0.001	——-	<0.001	<0.001	0.183	0.054	<0.001	<0.001
RIx	*r*	−0.602	0.307	−0.264	0.991	1	−0.358	0.066	−0.121	0.513	0.473
	p	<0.001	<0.001	<0.001	<0.001	——-	<0.001	0.206	0.064	<0.001	<0.001
Carotid applanation tonometry											
baSBP (mmHg)	*r*	−0.068	0.002	−0.032	0.090	0.104	0.293	0.366	−0.006	0.019	0.020
	p	0.222	0.489	0.362	0.155	0.122	<0.001	<0.001	0.475	0.416	0.412
baDBP (mmHg)	*r*	−0.218	0.065	−0.157	0.294	0.300	−0.434	−0.187	−0.362	0.312	0.315
	p	0.007	0.233	0.038	<0.001	<0.001	<0.001	0.019	<0.001	<0.001	<0.001
baMBP (mmHg)	*r*	0.101	0.086	0.001	−0.047	−0.060	−0.263	−0.297	−0.050	0.010	0.010
	p	0.128	0.167	0.496	0.301	0.251	0.002	<0.001	0.290	0.458	0.456
aoSBP (mmHg)	*r*	0.425	0.443	0.018	−0.053	−0.070	0.653	0.556	0.050	−0.164	−0.174
	p	<0.001	<0.001	0.407	0.244	0.182	<0.001	<0.001	0.262	0.018	0.013
aoDBP (mmHg)	*r*	−0.283	−0.007	−0.177	0.307	0.307	−0.410	−0.189	−0.334	0.325	0.320
	p	<0.001	0.464	0.010	<0.001	<0.001	<0.001	0.008	<0.001	<0.001	<0.001
AP (mmHg)	*r*	−0.496	0.079	−0.078	0.601	0.607	−0.750	−0.052	−0.291	0.736	0.726
	p	0.000	0.152	0.156	<0.001	<0.001	<0.001	0.253	<0.001	<0.001	<0.001
AIx (%)	*r*	−0.444	0.152	−0.044	0.652	0.658	−0.633	0.112	−0.261	0.827	0.804
	p	<0.001	0.023	0.284	<0.001	<0.001	<0.001	0.078	<0.001	<0.001	<0.001
SEVR	*r*	0.184	0.283	0.319	0.129	0.134	−0.038	0.206	0.183	0.241	0.255
	p	0.008	<0.001	<0.001	0.046	0.040	0.314	0.004	0.010	0.001	0.001
Pf (mmHg)	*r*	0.554	0.318	0.030	−0.358	−0.358	1	0.424	0.453	−0.628	−0.651
	p	<0.001	<0.001	0.353	<0.001	<0.001	——-	<0.001	<0.001	<0.001	<0.001

(Continued)

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TABLE 2 (Continued)

		Radial applanation tonometry					Carotid applanation tonometry				
		Pf (mmHg)	Pb (mmHg)	Pb AT (ms)	RM	RIx	Pf (mmHg)	Pb (mmHg)	Pb AT (ms)	RM	RIx
Pb (mmHg)	*r*	0.323	0.473	0.183	0.072	0.066	0.424	1	−0.041	0.352	0.358
	p	<0.001	<0.001	0.011	0.183	0.206	<0.001	—--	0.300	<0.001	<0.001
Pb AT (ms)	*r*	0.221	0.120	0.300	−0.128	−0.121	0.453	−0.041	1	−0.405	−0.438
	p	0.003	0.066	<0.001	0.054	0.064	<0.001	0.300	—--	<0.001	<0.001
RM	*r*	−0.316	0.127	0.076	0.527	0.513	−0.628	0.352	−0.405	1	0.990
	p	<0.001	0.056	0.171	<0.001	<0.001	<0.001	<0.001	<0.001	—--	<0.001
RIx	*r*	−0.301	0.105	0.093	0.481	0.473	−0.651	0.358	−0.438	0.990	1
	p	<0.001	0.094	0.121	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	—--

r, Pearson coefficient; SBP, PP, DBP, MBP, systolic, pulse, diastolic and mean blood pressure; ao, aortic; ba, brachial artery; Pf, central forward pulse pressure height; Pb, central backward pulse pressure height; PbAT, central backward arrival time; Aix, augmentation index; AP, central augmented pressure; SEVR, sub-endocardial viability ratio; RM, reflection magnitude; RIx, reflection index.

No women had carotid plaques, diabetes, or family history of premature CVD (data presented elsewhere) (7).

Wave separation analysis-derived indexes: Association with blood pressure levels and pulse wave analysis-derived indexes

Wave separation analysis-derived indexes (i.e., Pf, Pb, PbAT, RM, RIx) obtained through RT and CT showed significant associations ($p < 0.05$) with respect to baBP, aoBP levels, and PWA-derived indexes. As expected, Pf and Pb were positively associated with baSBP and aoSBP, which indicates that the greater the forward and backward wave components the greater the aoSBP (**Table 2**).

In general terms, there were statistically significant associations between the WSA- and PWA-derived indexes when considering RT and CT recordings. It is important to note though, when the WSA-derived indexes were compared to themselves (RT vs. CT recordings), despite the fact that the values showed statistically significant levels of association, the strengths of association were generally "moderate" (Pf: $r = 0.554$, $p < 0.001$; Pb: $r = 0.473$, $p < 0.001$; PbAT: $r = 0.3$, $p < 0.001$; RM, $r = 0.527$, $p < 0.001$; RIx, $r = 0.473$, $p < 0.001$) (**Table 2**).

Forward pressure

The levels of Pf and Pb were positively associated, which likely reflects the interrelationship between these parameters. In other words, a greater Pf component will determine a higher chance of wave reflections (a greater Pb), while a greater Pb component will raise the incident component (a greater Pf) by favoring transmission of wave reflections from the periphery to the center.

Conversely, the analysis between Pf and RM or RIx (parameters that assess the relative contribution of Pb to the resultant pressure wave) showed a negative association. In other words, the greater the Pf the smaller (relative) the contribution of Pb to the pulse pressure amplitude. Moreover, the associations between Pf and PWA-derived indexes were invariably negative, both when analyzing the "net" (AP, APHR75) or "relative" (AIx, AIxHR75) contribution of reflected waves (**Table 2**).

Of note, regardless of statistical significance ($p < 0.05$), the strength of association (r coefficient) between Pf and PWA-derived indexes was practically < 0.6 in all cases, having values ranging from "very weak" (r: 0.0–0.2), "weak" (r: 0.2–0.4) to "moderate" (r: 0.4–0.6) (**Table 2**).

Backward pressure (backward component arrival time)

As expected, Pb was positively associated with RM and RIx. Even though Pb was positively associated with APHR75 and AIxHR75, the strength of association was "very weak" ($r < 0.2$), which indicates that these parameters describe or characterize different hemodynamic phenomena (**Table 2**).

In addition, as predicted, a greater PbAT (late wave reflections arrival) was associated with a lower aoSBP, AP and AIx, and with a greater SEVR, with a strength of association for all being either "very weak" or "weak" (**Table 2**).

Reflection magnitude and reflection index

The levels of RM and RIx were significantly and positively associated with the aoSBP levels and with the PWA-derived indexes (AP, APHR75, Aix, and AIxHR75), with strengths of association that were "strong" (r: 0.6–0.8) or even "very strong" (r: 0.8–1.0). As a result, RM and RIx were the WSA-derived indexes that showed the strongest associations with PWA-derived indexes (i.e., AP and AIx) (**Table 2**).

Central aortic blood pressure (carotid and radial records) of non-pregnant, healthy pregnancy, and pregnancy-associated hypertension

Regardless of the recording method (CT or RT), aoSBP was elevated in women with PAH compared to NP and HP, confirming that the hemodynamic disturbances in this group of patients are not exclusively a peripheral phenomenon (i.e., brachial), but also a central (i.e., aortic) abnormality (**Table 3**). Women with PE showed a trend of presenting with higher aoSBP levels compared to women with GH; however, these differences were only statistically significant when these parameters were obtained by RT (**Table 3**). Consequently, a methodological factor (CT vs. RT) could also be playing a role in these observations, either amplifying or blunting potential existing differences in the aoSBP of the PAH subgroups.

Wave separate analysis-derived indexes of non-pregnant, healthy pregnancy, and pregnancy-associated hypertension

Forward pressure

While women with HP showed a lower Pf compared to NP, women with PAH showed higher Pf in comparison to both HP and NP (regardless of the measurement approach, i.e., CT or RT). These differences were particularly pronounced when using CT recordings (**Table 3**).

When separately assessing both hypertensive states (GH and PE), Pf values tended to be higher than those measured in women with HP. Notably, there were no statistical differences in Pf between GH and PE even when using different measurement modalities (**Table 3**).

Backward pressure

There was no single case in which PAH was associated with significant differences in Pb with respect to NP or HP. There were also no differences in PbAT, regardless of the recording technique (CT or RT).

However, according to the analysis of both hypertensive states, PE showed a tendency to present with higher Pb values than NP, HP and GH, as well as a trend of having faster wave reflection arrival (i.e., lower PbAT) (**Table 3**).

Reflection magnitude and reflection index

The analysis of RM and RIx showed similarities when using CT and RT recordings. PAH presented with lower RM and RIx compared to NP and HP, although these observations were only statistically significant when using RT-derived measurements, while the threshold of significance was not reached for CT recordings. On the other hand, GH and PE showed no differences in the analysis of these parameters (**Table 3**).

Discussion

Main findings

The present work, to our knowledge, is the first one to determine and compare WSA- and PWA-derived indexes in a group of healthy NP, and HP and PAH, by using two different approaches (RT and CT). The main contributions of this study are:

First, from a methodologic standpoint, despite the existence of positive associations between the same WSA-derived indexes obtained by RT or CT, the strength of association observed in each single parameter was no more than "moderate" (**Table 2**). Accordingly, special care must be taken when interpreting WSA-derived indexes, as the levels of these parameters are not the same when using RT vs. CT and these techniques cannot be used interchangeably.

Second, while Pf was positively associated with the Pb level, it was negatively (very weakly, weakly, and moderately) associated with the levels of PWA-derived indexes, both when analyzing the "net" (AP, APHR75) or the "relative" (AIx, AIxHR75) contribution to wave reflections (**Table 2**).

Third, Pb was positively associated with AP and AIx, although the strength of association was very weak ($r < 0.2$). This provides evidence that indexes of "wave reflection" obtained by WSA and PWA are, in fact, not identifying or describing the same physiological characteristics (**Table 2**). Therefore, despite these parameters potentially providing complementary information about wave reflections, they hold little relationship and the information derived from these parameters should be used cautiously.

Fourth, PAH had characteristically high Pf compared to NP and HP (regardless the site of arterial tonometry recording). Subgroup analysis revealed that this finding was in fact shared by both subtypes of hypertensive states (GH and PE) (**Table 3**), and no differences were observed between these conditions. Consequently, the PAH state, to a good extent, is the result of a large anterograde pressure component generated by the LV itself in combination with its interaction with the arterial and microcirculatory systems, and not simply by an increase in the retrograde pressure component (wave reflections), as previously suggested. Surprisingly, PAH was not clearly associated with significant differences in Pb or PbAT compared to NP and HP, regardless of the tonometry recording site (**Table 3**). Thus, there is no consistent evidence that would indicate that PAH status (as a group) would represent a state characterized by higher levels of wave reflections, either by an increase in the magnitude or by an early arrival of the wave reflection from the periphery to the center. However, when analyzing PE, this group did show a trend of presenting with higher Pb than NP, HP and GH, and an earlier return of wave reflections (lower PbAT) (**Table 3**). It is important to note that this observation occurred without clear statistical significance in all comparisons and further

TABLE 3 Carotid and radial applanation tonometry-derived central blood pressure levels and waveform related parameters: comparison after adjustments (ANCOVA: 3 and 4 groups).

Variables: 3 groups		After adjustment					Pairwise comparisons		
		MV	SE	LL	UL		NP vs. HP	NP vs. PAH	HP vs. PAH
Carotid applanation tonometry									
aoSBP [mmHg]	NP	109.43	1.03	107.40	111.46	**MD**	−0.048	−9.760	−9.712
	HP	109.48	5.68	98.28	120.68	**P**	0.497	0.013	0.085
	PAH	119.19	4.15	111.00	127.38	**Boot. P**	0.497	0.028	0.105
Pf [mmHg]	NP	42.63	1.14	40.38	44.88	**MD**	6.570	−11.005	−17.575
	HP	36.06	6.58	23.07	49.05	**P**	0.164	0.009	0.013
	PAH	53.63	4.40	44.94	62.32	**Boot. P**	0.148	0.019	0.015
Pb [mmHg]	NP	16.39	0.37	15.65	17.13	**MD**	0.540	−1.745	−2.285
	HP	15.85	2.15	11.60	20.10	**P**	0.403	0.125	0.188
	PAH	18.13	1.44	15.29	20.98	**Boot. P**	0.441	0.160	0.233
Pb AT [ms]	NP	269.26	2.67	264.00	274.52	**MD**	2.154	1.414	−0.740
	HP	267.11	15.33	236.84	297.37	**P**	0.445	0.448	0.484
	PAH	267.85	10.26	247.60	288.10	**Boot. P**	0.424	0.458	0.487
RM	NP	0.413	0.010	0.394	0.433	**MD**	−0.049	0.048	0.096
	HP	0.462	0.056	0.351	0.573	**P**	0.197	0.115	0.076
	PAH	0.366	0.038	0.291	0.440	**Boot. P**	0.294	0.180	0.173
RIx	NP	0.287	0.005	0.277	0.297	**MD**	−0.021	0.030	0.050
	HP	0.308	0.028	0.252	0.363	**P**	0.239	0.066	0.069
	PAH	0.257	0.019	0.220	0.294	**Boot. P**	0.322	0.149	0.148
Radial applanation tonometry									
aoSBP [mmHg]	NP	102.810	0.532	101.763	103.856	**MD**	5.377	−8.673	−14.050
	HP	97.433	3.160	91.218	103.648	**P**	0.047	0.001	0.000
	PAH	111.483	2.603	106.364	116.602	**Boot. P**	0.020	0.002	0.000
Pf [mmHg]	NP	29.906	0.447	29.027	30.785	**MD**	1.501	−4.222	−5.723
	HP	28.405	2.633	23.227	33.583	**P**	0.287	0.029	0.048
	PAH	34.128	2.167	29.866	38.389	**Boot. P**	0.296	0.006	0.029
Pb [mmHg]	NP	13.797	0.185	13.433	14.161	**MD**	−0.185	0.434	0.619
	HP	13.982	1.090	11.838	16.126	**P**	0.434	0.319	0.331
	PAH	13.363	0.897	11.599	15.127	**Boot. P**	0.433	0.326	0.326
Pb AT [ms]	NP	251.908	1.351	249.250	254.565	**MD**	9.470	7.020	−2.450
	HP	242.437	7.958	226.786	258.089	**P**	0.121	0.148	0.407
	PAH	244.888	6.550	232.006	257.770	**Boot. P**	0.129	0.084	0.400
RM	NP	0.481	0.006	0.469	0.492	**MD**	−0.034	0.097	0.131
	HP	0.515	0.035	0.447	0.583	**P**	0.332	0.001	0.004
	PAH	0.384	0.029	0.327	0.440	**Boot. P**	0.485	0.002	0.016
RIx	NP	0.321	0.003	0.315	0.326	**MD**	−0.015	0.041	0.056*
	HP	0.335	0.015	0.305	0.366	**P**	0.171	0.001	0.003
	PAH	0.279	0.013	0.254	0.304	**Boot. P**	0.214	<0.001	0.004

Variables: 4 groups		After adjustment					Pairwise comparisons					
		MV	SE	LL	UL		NP vs. HP	NP vs. GH	NP vs. PE	HP vs. GH	HP vs. PE	GH vs. PE
Carotid applanation tonometry												
aoSBP [mmHg]	NP	109.4	1.0	107.4	111.5	**MD**	−0.067	−7.365	−12.745	−7.298	−12.678	−5.380
	HP	109.5	5.7	98.3	120.7	**P**	0.495	0.091	0.018	0.177	0.062	0.241
	GE	116.8	5.4	106.2	127.4	**Boot. P**	0.497	0.169	0.004	0.233	0.052	0.269
	PE	122.2	5.9	110.5	133.9		—-	—-	—-	—-	—-	—-

(Continued)

TABLE 3 (Continued)

Variables: 4 groups		After adjustment					Pairwise comparisons					
		MV	SE	LL	UL		NP vs. HP	NP vs. GH	NP vs. PE	HP vs. GH	HP vs. PE	GH vs. PE
Pf [mmHg]	NP	42.6	1.1	40.4	44.9	**MD**	6.624	−14.185	−7.020	−20.809	−13.644	7.166
	HP	36.0	6.6	23.0	49.0	**P**	0.162	0.008	0.138	0.009	0.066	0.187
	GH	56.8	5.7	45.6	68.0	**Boot. P**	0.139	0.019	0.143	0.011	0.066	0.208
	PE	49.7	6.3	37.3	62.0		—-	—-	—-	—-	—-	—-
Pb [mmHg]	NP	16.4	0.4	15.6	17.1	**MD**	0.510	0.025	−3.964	−0.484	−4.474	−3.990
	HP	15.9	2.1	11.6	20.1	**P**	0.408	0.495	0.030	0.432	0.065	0.065
	GH	16.4	1.9	12.7	20.0	**Boot. P**	0.424	0.496	0.021	0.448	0.069	0.097
	PE	20.3	2.0	16.3	24.4		—-	—-	—-	—-	—-	—-
Pb AT [ms]	NP	269.3	2.7	264.1	274.5	**MD**	2.355	−10.447	16.281	−12.803	13.925	26.728
	HP	266.9	15.3	236.8	297.1	**P**	0.440	0.221	0.138	0.263	0.253	0.077
	GH	279.7	13.2	253.7	305.8	**Boot. P**	0.413	0.314	0.028	0.298	0.157	0.120
	PE	253.0	14.6	224.3	281.8		—-	—-	—-	—-	—-	—-
RM	NP	0.41	0.01	0.39	0.43	**MD**	−0.050	0.105	−0.025	0.155	0.025	−0.130
	HP	0.46	0.06	0.35	0.57	**P**	0.191	0.017	0.325	0.018	0.372	0.029
	GE	0.31	0.05	0.21	0.40	**Boot. P**	0.291	0.071	0.359	0.088	0.412	0.094
	PE	0.44	0.05	0.33	0.54		—-	—-	—-	—-	—-	—-
RIx	NP	0.29	0.00	0.28	0.30	**MD**	−0.021	0.062	−0.010	0.083	0.011	−0.072
	HP	0.31	0.03	0.25	0.36	**P**	0.231	0.007	0.356	0.013	0.388	0.018
	GE	0.23	0.02	0.18	0.27	**Boot. P**	0.316	0.045	0.379	0.068	0.412	0.066
	PE	0.30	0.03	0.24	0.35		—-	—-	—-	—-	—-	—-
Radial applanation tonometry												
aoSBP [mmHg]	NP	102.80	0.53	101.76	103.84	**MD**	5.340	−3.095	−14.634	−8.435	−19.974	−11.539
	HP	97.46	3.14	91.28	103.64	**p**	0.047	0.192	<0.001	0.038	<0.001	0.009
	GE	105.90	3.51	98.99	112.80	**Boot. P**	0.025	0.217	<0.001	0.035	<0.001	0.009
	PE	117.44	3.62	110.32	124.54		—-	—-	—-	—-	—-	—-
Pf [mmHg]	NP	29.90	0.45	29.02	30.78	**MD**	1.494	−3.040	−5.484	−4.534	−6.978	−2.444
	HP	28.41	2.64	23.23	33.59	**p**	0.288	0.154	0.038	0.127	0.042	0.276
	GH	32.94	2.94	27.16	38.73	**Boot. P**	0.274	0.055	0.009	0.084	0.021	0.205
	PE	35.39	3.03	29.43	41.35		—-	—-	—-	—-	—-	—-
Pb [mmHg]	NP	13.80	0.18	13.43	14.16	**MD**	−0.192	1.541	−0.749	1.733	−0.557	−2.290
	HP	13.99	1.09	11.85	16.13	**p**	0.431	0.106	0.278	0.146	0.369	0.089
	GH	12.25	1.22	9.86	14.65	**Boot. P**	0.437	0.034	0.307	0.113	0.375	0.069
	PE	14.54	1.25	12.08	17.01		—-	—-	—-	—-	—-	—-
Pb AT [ms]	NP	251.91	1.35	249.24	254.57	**MD**	9.461	8.472	5.468	−0.989	−3.993	−3.004
	HP	242.44	7.97	226.77	258.12	**P**	0.121	0.174	0.278	0.467	0.372	0.404
	GH	243.43	8.90	225.94	260.93	**Boot. P**	0.116	0.081	0.234	0.462	0.368	0.384
	PE	246.44	9.17	228.41	264.46		—-	—-	—-	—-	—-	—-
RM	NP	0.481	0.006	0.469	0.492	**MD**	−0.034	0.113	0.080	0.147	0.115	−0.032
	HP	0.515	0.035	0.447	0.583	**p**	0.166	0.002	0.024	0.003	0.015	0.274
	GE	0.368	0.039	0.292	0.444	**Boot. P**	0.254	0.001	0.023	0.005	0.027	0.235
	PE	0.400	0.040	0.322	0.479		—-	—-	—-	—-	—-	—-
RIx	NP	0.321	0.003	0.315	0.326	**MD**	−0.015	0.050	0.033	0.065	0.048	−0.017
	HP	0.335	0.015	0.305	0.366	**p**	0.170	0.002	0.035	0.003	0.022	0.243
	GE	0.271	0.017	0.237	0.305	**Boot. P**	0.244	<0.001	0.026	0.001	0.033	0.200
	PE	0.288	0.018	0.253	0.323		—-	—-	—-	—-	—-	—-

NP, non-pregnant women; HP, healthy pregnant women; PAH, pregnancy-associated hypertension; GH, gestational hypertension; PE, preeclampsia; MV, mean value; SE, standard error; LL and UL, 95% confidence interval lower limit and upper limit; Boot, bootstrapping; *p*, *p*-value; aoSBP, central SBP; Pf, central forward pulse pressure Height; Pb, central backward pulse pressure height; PbAT, central backward arrival time; RM, reflection magnitude; RIx, reflection index; MD, mean difference.

studies would be needed to clarify this result. Finally, PAH status showed a trend of presenting lower RM and RIx than NP and HP, with no differences between PE and GH. When analyzing all this data together, it seems that WSA does not support the idea that PAH represents a consistent high wave reflection hemodynamic state, but to the contrary, a "high Pf state."

In normal conditions, intermittent forward pressure waves generated by the LV collide with reflection sites located throughout the arterial tree, resulting in transmitted pressure waves (forward resultants) and pressure wave reflections (backward resultants). One of the most important reflection sources resides in the normal "stiffness gradient" of the arterial system (the farther from the LV, the stiffer the arteries get). The stiffness gradient functions as a filter of the forward pressure waves, protecting the microcirculation from high energy pressure transmission by creating wave reflections at the level where the great complaint arteries (elastic arteries) transition to the relatively smaller and stiffer muscular arteries (34). We have shown recently that when compared with NP, HP was associated with a preserved "center-to-periphery" arterial stiffness gradient (evaluated through pulse wave velocity [PWV] ratio) despite a significant drop in central aortic stiffness, quantified as the quotient between carotid-femoral PWV and carotid-radial PWV. In addition, when compared with NP and HP, PAH was associated with an "exaggerated rise" in the PWV ratio (attenuation or even reversal of the gradient), and thus, leading to a dissipation of one of the potential sources of wave reflections and microcirculation protection (7). Altogether, these observations agree with our current study. By using a methodology that is not related directly with PWV measurements (arterial stiffness assessment), our study reveals that the levels of wave reflections assessed by RM and RIx are significantly reduced in PAH, which is conceptually consistent with the aforementioned. Thus, despite the fact that women with PAH showed a higher Pf, which in turn could be associated with a higher aortic stiffness (hyperdynamic LV encountering a relatively stiff aorta during systole), this did not translate to an invariably higher Pb.

Similarly, both RM and RIx indexes also provide information about the ability of the cardiovascular system to filter excessive pressure energy transmission to certain microcirculatory beds. As mentioned, from a physiologic standpoint, the reduced RM and RIx observed in PAH would both have impaired protective effects on the distal microcirculation, potentially leading to excessive barotrauma and shear forces which would result in damage to peripheral vascular beds (e.g., placental circulation). In the setting of excessive pulsatile pressure, an increased arteriolar myogenic response could function as the last resource to protect the distal organ, but at the expense of reducing the distal peripheral perfusing blood flow. Given the fetal metabolic needs, the placenta must operate at very high flow/low vascular resistance, making it second only to the kidney regarding blood flow rates per unit of tissue mass (11). Other low-resistance vascular beds, such as renal, hepatic, and cerebral circulation can also be at risk of excessive pulsatility, since microvascular pressure is also directly coupled with aoBP fluctuations (3). Hence, the transmission of a higher pulsatile pressure into the placental and other low-resistance microcirculations might be highly likely in the setting of attenuation of RM or RIx, leading potentially to secondary placental dysfunction (e.g., intrauterine growth restriction), hepatic damage (e.g., elevated liver enzymes, hematoma), and renal damage (e.g., proteinuria), among other PE-related complications.

Strengths and limitations

Our results should be analyzed in the context of both its strengths and limitations. To the best of our knowledge, there are no studies in the literature that have evaluated WSA-related indexes in HP and PAH. Another important strength of this study is the robustness of the methodology employed to assess WSA, utilizing two different approaches: CT and RT, which consists in a simple, non-invasive, robust, and reproducible methodology. In fact, the use of applanation tonometry has been largely validated and is regarded as the "gold standard" method for measuring waveform-derived indexes.

This study has certain limitations, however. First, since this is a cross-sectional study, it provides no data on longitudinal pregnancy-related temporal variations in the variables of interest. Second, in this work, the concept of WSA-derived indexes was presented as "static or unchanged" rather than the composite of (i) "fixed or stable" (e.g., age-dependent vascular [intrinsic] stiffness level) and (ii) "variable or adjustable" (e.g., endothelial and vascular smooth muscle ability to temporally adjust the RM or RIx level) (35). The systematization of recording conditions is necessary to evaluate WSA- and PWA-derived indexes considering the existence of modulating factors. In this work, to systematize the measurement and to minimize the impact of sources of variability, RT and CT recordings were determined at rest and under stable hemodynamic conditions, while only recordings with high operator index values (>95%) were accepted for further analysis. Third, the sample size of our group of pregnant women is relatively small. To overcome this limitation, we used bootstrapping, a statistical method that creates a new sample of observations of the variables by randomized re-sampling, with replacement based on the original observations. This method has its own advantages and disadvantages, but in this context, the biggest mistake that we can make is not generating a type I error (finding differences when in reality there are none), but, in fact, generating a type 2 error

(not finding differences when in fact there are). Thus, we have taken the "conservative" approach, thereby, potentially missing significant differences that truly exist. Finally, as this study is considered exploratory and hypotheses generating (e.g., multiple correlations performed), larger sample size and/or prospective analyses will be indicated to assess and explore meaningful parameters in these patients.

Conclusion

First, despite the existence of a positive association between one single WSA-derived index obtained by CT and RT, these associations were, in general terms, of moderate strength, so these approaches cannot be used interchangeably. Second, Pf was positively associated with Pb and negatively with PWA-derived indexes, both when analyzing the "net" (AP, APHR75) and the "relative" (AIx, AIxHR75) contribution of wave reflections. Third, Pb was positively associated with AP and AIx, although the strength of this association was very weak, which indicates that indexes of wave reflections obtained by WSA and PWA do not identify similar physiologic hemodynamic characteristics.

Fourth, PAH status was associated with higher Pf compared to HP and NP, regardless of the tonometry recording site. Both hypertensive states (GH and PE) were associated with higher Pf compared to HP, without significant differences with regards to Pb or PbAT when compared to NP or HP. However, women with PE showed a trend of presenting with higher Pb in comparison to NP, HP, and GH, with a potentially faster arrival of wave reflection components. Through our results, the use of WSA supports the idea that hypertension in women with PAH is mainly explained by a higher Pf rather than increased wave reflections.

Data availability statement

The original contributions presented in this study are included in the article/**Supplementary material**, further inquiries can be directed to the corresponding author/s.

Ethics statement

The studies involving human participants were reviewed and approved by Comité de Ética del Centro Hospitalario Pereira-Rossell. The patients/participants provided their written informed consent to participate in this study.

Author contributions

MP, JT, DB, and YZ contributed to conception and design of the study. JT, YZ, and DB performed the cardiovascular non-invasive recordings and constructed and organized the database. YZ and DB performed the statistical analysis. MP, JT, JB, DB, and YZ wrote the first draft of the manuscript. JB, CS, and AD performed the revisions and critically discussed the complete manuscript. All authors read and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.997452/full#supplementary-material

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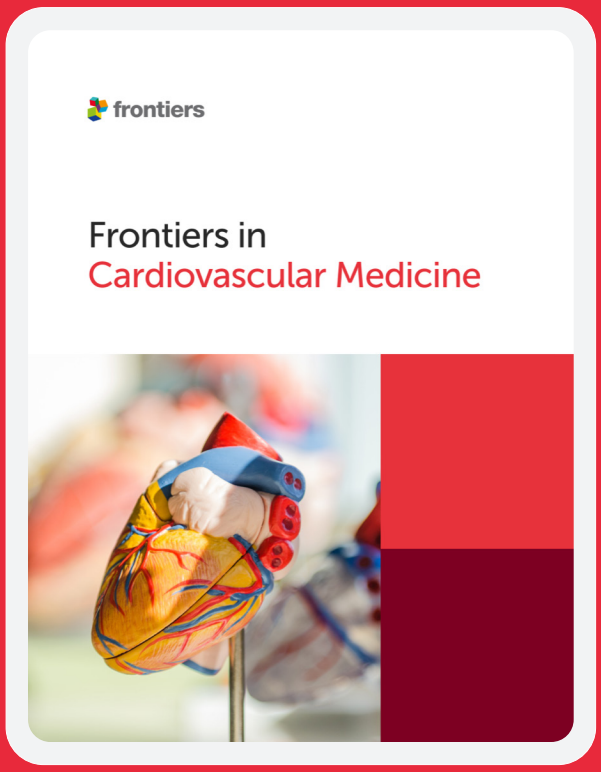

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