*Report*

# Management and Outcomes of Pregnancy in Patients with Pulmonary Arterial Hypertension Associated with Congenital Heart Disease

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**ABSTRACT**

**Background**: Pregnant women with pulmonary arterial hypertension associated with congenital heart diseases (PAH-CHD) have a high incidence of mortality and adverse outcomes for mother and child.
**Methods**: We retrospectively examined the treatment strategies and the outcomes of pregnancy in patients with pulmonary arterial hypertension managed at a single clinical hospital from 2009 to 2018.
**Results**: Analysis of all 102 patients with PAH-CHD in pregnancy showed that maternal and newborn death from the disease was low (<3%, 3/102) compared to rates previously reported. Although patients with mild pulmonary hypertension can deliver a newborn safely, those with moderate to severe pulmonary artery pressure (PAP), and high functional class tend to have a high risk of heart failure. Medications were selectively administered to patients with more severe disease, and it was, therefore, challenging to make a universal statement on their benefit, but they appear having some benefits in improving birth outcomes for mother and child. While some treatments such as anti-coagulant therapy during pregnancy, and oxytocin after delivery, did not improve the health outcome of pregnant women but seemed to provide some benefits to the newborns.
**Conclusion**: Our retrospective analysis of existing clinical data provides preliminary results for further studies to formally evaluate the efficacy of clinical management of patients with pulmonary arterial hypertension.

**KEYWORDS**

**C**ongenital heart disease, pulmonary arterial hypertension, pregnant women

## INTRODUCTION

Pulmonary arterial hypertension (PAH) is "a syndrome resulting from restricted flow through the pulmonary arterial circulation resulting in increased pulmonary vascular resistance and ultimately in the right heart failure" (1), according to the American Heart Association (2009). It is a common complication of congenital heart disease (CHD) (2). A large European Registry and database of EuroHeart Survey estimate the overall prevalence of PAH in adult patients with CHD is 4% (3,4). Individuals with PAH-CHD are associated with a high risk of adverse outcomes in pregnancy. The maternal mortality rate in patients with PAH had been estimated to be approximately 30-36% (5). During pregnancy, the change in hemodynamic and endocrine results in elevated pulmonary vascular resistance, which appears detrimental to these patients. Without timely and effecttive treatment, the pregnant patients with PAH-CHD often end up with right ventricular (RV) failure and, ultimately, death (6, 7). Therefore, pregnancy should be discouraged for individuals at high risk of these conditions (1, 8).

While still lacking effective drugs and research methodology (9), the maternal and fetal outcomes of patients with PAH-CHD have improved over the past decades (10, 11). The improved outcome is mostly due to the development of multidisciplinary clinical management, improvements in obstetric and anesthetic management, and an increased understanding of cardiopulmonary pathophysiology, and in particular, with the development of new advanced therapies for PAH. As a less developed country, Chinese families have a strong preference for a woman having a child,

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and many women with PAH-CHD chose to carry and deliver a baby, and women with PAH-CHD still choose to have a baby. To better understand whether contemporary therapies for pregnant patients with PAH-CHD have improved the maternal and fetal outcomes, we collected data for patients treated at the Second Xiangya Hospital of Central South University in China from 2009 to 2018. We aimed to assess the maternal and fetal outcomes of pregnant patients with PAH-CHD in association with management strategies at the hospital and to obtain information to facilitate the management of pregnant patients.

## METHODS

### Dataset

The data used for the analysis included pregnant patients with PAH-CHD treated at the Second Xiangya Hospital of Central South University from January 2009 to December 2018. All patients were identified through a review of the hospital database. The diagnosis was established based on clinical history, physical examination, and echocardiography examination performed during pregnancy. Patients who were diagnosed with PAH-CHD before or during pregnancy were selected. We reviewed the medical records of all patients and collected information on the gestational age at presentation, echocardiograph, PAH-specific therapy received methods of delivery, complications, and maternal and fetal outcomes. We retrospectively analyzed the factors for association with heart failure and examined the impact of targeted treatment on maternal and fetal outcomes.

The Ethics Committee of the Second Xiangya Hospital of Central South University approved the study and all the medical records of these patients are stored in the hospital.

### Data analysis

We carried out descriptive studies and calculated mean and SD for continuous variables and frequency for dichotomous variables. We performed statistical tests using Student's T-test, Chi-Squared, or Fisher's exact test as appropriate to determine if there were any significant associations. The data analyses were performed using SPSS Statistics 19 (Las Vegas, Nevada, USA)

## RESULTS

### Patients' baseline characteristics

Table 1 presents the characteristics of patients with PAH at baseline. There were 102 pregnant patients identified, of which 21% (21/102) experienced heart fail-ure, including three patients who ended with maternal deaths. Overall, patients were very similar in the mean age, gravidity, and parity between patients whose pregnancy resulted in maternal deaths. The mean age was 28.19 years and 27.52 years in patients of PAH-CHD with and without heart failure, respectively. While the average of gravidity was around two, the mean number of parities was only 0.3 in both groups; there was a similar pattern in the time of diagnosis before or during pregnancy.

**Table 1.** Baseline characteristic of PAH-CHD patient with or without heart failure

| | No heat failure (N=81) | | | Heart failure (N=21) | | | |
|---|---|---|---|---|---|---|---|
| | Mean | %/Mean | SD | Mean | %/Mean | SD | P |
| Age (years) | 81 | 28.19 | 5.51 | 21 | 27.52 | 6.37 | 0.424 |
| Gravidity | 81 | 2.15 | 1.25 | 21 | 1.9 | 1.3 | 0.850 |
| Parity | 81 | 0.32 | 0.52 | 21 | 0.33 | 0.65 | 0.43 |
| SpO2 during pregnancy (%) | 81 | 94.94 | 5.09 | 21 | 88.24 | 7.78 | <0.001 |
| Parity | 81 | 0.32 | 0.52 | 21 | 0.33 | 0.65 | 0.430 |
| **Type of cardiac malformation** | | | | | | | |
| Ventricular septal defect (VSD) | 31 | 0.38 | | 11 | 0.52 | | 0.250 |
| Atrial septal defect (ASD) | 31 | 0.38 | | 5 | 0.24 | | |
| Patent ductus arteriosus (PDA) | 6 | 0.07 | | 1 | 0.05 | | |
| Tetralogy of Fallot (TOF) | 6 | 0.07 | | 0 | 0.00 | | |
| Valvular heart disease | 3 | 0.04 | | 1 | 0.05 | | |
| Single ventricle | 1 | 0.01 | | 2 | 0.10 | | |
| Single atrium | 1 | 0.01 | | 1 | 0.05 | | |
| Marfa's syndrome | 2 | 0.02 | | 0 | 0.00 | | |
| **Time of diagnosis of CHD-PAH** | | | | | | | |
| Before pregnancy | 22 | 0.28 | | 4 | 0.19 | | 0.579 |
| During pregnancy | 59 | 0.73 | | 17 | 0.81 | | |
| Surgery before pregnancy | 27 | 0.33 | | 3 | 0.14 | | 0.111 |
| **NYHA classification** | | | | | | | |
| I-II | 62 | 0.77 | | 1 | 0.05 | | |
| III-IV | 19 | 0.23 | | 20 | 0.95 | | |
| **Pulmonary artery pressure (PAP)** | | | | | | | |
| 25-49(mmHg) | 68 | 0.84 | | 9 | 0.43 | | ＜0.001 |
| 50-79(mmHg) | 7 | 0.09 | | 9 | 0.43 | | |
| ≥80(mmHg) | 6 | 0.07 | | 3 | 0.14 | | |

* NYHA, New York Heart Association functional class:

1) Class I - No symptoms and no limitation in ordinary physical activity, e.g., shortness of breath when walking, climbing stairs, etc.
2) Class II - Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
3) Class III - Marked limitation in an activity due to symptoms, even during less-than-ordinary activity, e.g., walking short distances (20—100 m). Comfortable only at rest.
4) Class IV - Severe limitations. Experiences symptoms even while at rest — mostly bedbound patients.

Several baseline factors appeared different between individuals with and without heart failure. Both ventricular septal defect (VSD) and arterial septal defect (ASD) occurred in 38% of patients without heart failure, and occurred at 52% and 23% in the patients with heart failure. In addition, pregnant patients with heart failure appeared less likely to have surgery before pregnancy (14 %) than those (33%) without heart failure. NYHA functional class III-IV accounted for 95% of patients with heart failure and 23% of the patients without heart failure. The distribution of pulmonary artery pressure (PAP) was also significantly different between individuals with and without heart failure (Table 1). Patients without heart failure were more likely associated with low PAP at 25-49 mmHg (84%), which was a much higher prevalence than patients with heart failure having PAP at 25-49 (43%).

**Aadvanced therapy and maternal and birth out-comes**

Table 2 presents the management of patients with PAH-CHD and methods of the newborn delivery by heart failure. Majority of patients with heart failure had used prostaglandin (71%, 15/21), sildenafil (52%, 11/21), and diuretics (71%, 15/21), while corresponding usages were 21% (17/81), 14% (11/81) and 30% (24/81) in individuals without heart failure. Antithrombotic treatment was also more frequently used (52%, 11/21) in individuals without heart failure. These differences may indicate selective use of the advanced therapy according to the disease severity at baseline, and should not be interpreted as treatment effect. Also, the majority of patients (81-86%) used oxytocin regardless of heart failure.

**Table 2.** Managements of PAH-CHD patients with or without heart failure

| | No heart failure (N=81) | | Heart failure (N=21) | | |
|---|---|---|---|---|---|
| | N | % | N | % | P |
| **Advanced therapy for PAH** | | | | | |
| Nitric oxide | 0 | 0 | 2 | 0.1 | 0.041 |
| prostaglandin | 17 | 0.21 | 15 | 0.71 | <0.001 |
| Sildenafil | 11 | 0.14 | 11 | 0.52 | <0.001 |
| Diuretics | 24 | 0.30 | 15 | 0.71 | <0.001 |
| Calcium channel blockers | 1 | 0.01 | 2 | 0.1 | 0.107 |
| Antithrombotic therapy | 27 | 0.33 | 11 | 0.52 | 0.132 |
| Oxytocin | 70 | 0.86 | 17 | 0.81 | 0.504 |
| Admission to ICU | 20 | 0.25 | 18 | 0.86 | <0.001 |
| **Method of delivery** | | | | | |
| Abortion | 9 | 0.11 | 0 | 0 | 0.048 |
| Vaginal | 10 | 0.12 | 0 | 0 | 0.007 |
| Cesarean section | 62 | 0.77 | 21 | 1 | 0.048 |
| **Anesthesia** | | | | | |
| N/A | 0 | 0.11 | 0 | NA | |
| Regional Anesthesia | 22 | 0.27 | 5 | 0.24 | 0.094 |
| General Anesthesia | 50 | 0.62 | 16 | 0.2 | 0.138 |

The method of delivery was quite different between two groups of patients. All 21 patients with heart failure had a Caesarean section, while 77% of patients without heart failure had Caesarean section delivery. This might be due to the severity of disease in patients, because patients with heart failure had worse conditions at baseline (Table 1).

Table 3 presents the maternal and fetal outcomes by heart failure in pregnant patients with PAH. Three maternal deaths (3/21; 14%) occurred, and all were in patients with heart failure, and they died on day 6, 7, and 8 after delivery. There were 21 (20.59%) patients whose pregnancy ended with miscarriage; three (14%, n=21) were from patients with heart failure, and 18 (22%, n=81) were from patients without heart failure.

While some pregnancy complications seemed different in patients with or without heart failure, but only the pulmonary infection were different (Table 3). We noted some differences between patients with heart failure and those without in the outcomes such as pulmonary infections (33% vs. 6%), fetal growth restriction (19% vs. 7%), preeclampsia (10% vs. 5%), premature delivery (43% vs. 25%), and newborn death (10% vs. 6%) , these were not significantly different, which is likely due to the small sample size. Other pregnancy complications including pulmonary embolism and postpartum hemorrhage appeared similar in both groups, but the rates of occurrence were quite low (<=5%).

In China, fetuses delivered before 28 weeks are classified as abortions, 21 patients who failed to continue their pregnancy past 28 weeks were excluded for analysis of birth outcomes, but they were not counted as newborn deaths. We noted that patients with heart failure tend to have a low birth weight (mean=2312.78; SD=561.77) and poorer Apgar score at 1 minute (Mean=6.61; SD=2.62), both were below the normal weight (2500g) and healthy Apgar score (at or above 7).

**Table 3.** Maternal and birth outcomes of PAH-CHD patients by heart failure

| | No heart failure (N=81) | | | Heart failure (N=21) | | | |
|---|---|---|---|---|---|---|---|
| | N | %/Mean | SD | N | %/Mean | SD | P |
| **Maternal outcomes** | | | | | | | |
| Maternal death | 0 | 0.00 | | 3 | 0.14 | | 0.008 |
| Pulmonary infection | 5 | 0.06 | | 7 | 0.33 | | 0.002 |
| Pulmonary embolism | 0 | 0.00 | | 1 | 0.05 | | 0.206 |
| Preeclampsia | 4 | 0.05 | | 2 | 0.10 | | 0.600 |
| Fetal growth restriction | 6 | 0.07 | | 4 | 0.19 | | 0.209 |
| Postpartum hemorrhage | 2 | 0.02 | | 1 | 0.05 | | 0.503 |
| Miscarriage | 18 | 0.22 | | 3 | 0.14 | | 0.248 |
| Fetal malformation | 4 | 0.05 | | 1 | 0.05 | | 1.000 |
| Premature delivery | 20 | 0.25 | | 9 | 0.43 | | 0.248 |
| Newborn death | 5 | 0.06 | | 2 | 0.10 | | 0.648 |
| Newborn weight (g) | 63 | 2705 | 815 | 18 | 2313 | 562 | 0.059 |
| Apgar score 1 minute | 63 | 7.72 | 2.51 | 18 | 6.61 | 2.62 | 0.104 |
| Apgar score 5 minute | 63 | 9.08 | 2.71 | 18 | 8.28 | 3.12 | 0.288 |

* Patients who delivered before 28 gestational weeks were excluded as abortion (n=21); Miscarriage, delivery before 28 gestational weeks; premature delivery, delivered between 28-37 gestational weeks.

### Patient characteristic associated with maternal and birth outcomes

Because NYHA functional class was different between the statuses of heart failure, we examined the maternal and newborn outcomes by NYHA functional class at baseline. We noted a marked difference between NYHA functional class III-IV (n=39) and I-II (n=63) in pregnant complications and outcomes such as premature delivery (44% vs. 19%), pulmonary infections (18% vs. 8%), fetal growth restriction (13% vs. 8%), malformation (8% vs. 3%), preeclampsia (8% vs. 5%), and embolism (3% vs. 0%) (Table 4).

We did not note differences in other pregnant outcomes, in particular, miscarriage between functional classes because the frequency of miscarriage (21%) was equally common in both groups. The functional class appeared affecting the newborn outcomes in birth weight and poorer Apgar scores. Patients with HYHA functional class of III-IV tend to have babies with lower birth weight (Mean=2,318g, SD= 624), below the normal birth weight defined as 2,500g, and poorer Apgar score at 1 minute, which the mean score was 6.61, lower than the healthy level of 7.

Different from NYHA functional class, an elevated level of PAP was associated with having a miscarriage and premature delivery (Table 5). We noted a marked difference between different level of PAP such as miscarriage (12% vs. 25% vs. 33%) and premature delivery (26% vs. 44% vs. 22%).

**Table 4.** Maternal and newborn outcomes of PAH-CHD patients by NYHA functional class

| | NYHA I-II(n=63) | | | NYHA III-IV(n=39) | | | |
|---|---|---|---|---|---|---|---|
| | N | %/Mean | SD | N | %/Mean | SD | P |
| Maternal death | 0 | 0.00 | | 3 | 0.08 | | 0.053 |
| Maternal pulmonary infection | 5 | 0.08 | | 7 | 0.18 | | 0.204 |
| Maternal pulmonary embolism | 0 | 0.00 | | 1 | 0.03 | | 0.382 |
| Preeclampsia | 3 | 0.05 | | 3 | 0.08 | | 0.672 |
| Fetal growth restriction | 5 | 0.08 | | 5 | 0.13 | | 0.500 |
| Postpartum hemorrhage | 2 | 0.03 | | 1 | 0.03 | | 1.000 |
| Miscarriage | 13 | 0.21 | | 8 | 0.21 | | 0.019 |
| Fetal malformation | 2 | 0.03 | | 3 | 0.08 | | 0.368 |
| Premature delivery | 12 | 0.19 | | 17 | 0.44 | | 0.019 |
| Newborn death | 3 | 0.05 | | 4 | 0.10 | | 0.419 |
| Newborn weight (g) | 50 | 2804 | 815 | 31 | 2319 | 624 | 0.006 |
| Apgar score 1 minute | 50 | 8.01 | 2.27 | 31 | 6.61 | 2.79 | 0.016 |
| Apgar score 5 minute | 50 | 9.34 | 2.40 | 31 | 8.19 | 3.29 | 0.074 |

* Patients who delivered before 28 gestational weeks were excluded as abortion (n=21).

### Management of patients with maternal and birth outcomes

We examined the use of medications in managing the clinical symptoms in patients, maternal and fetal outcomes, and birth outcomes. Three medications were used on patients, prostacyclin analogs (prostaglandin), sildenafil, and diuretics. The use of prostaglandin appeared higher in patients with more severe NYHA functional class, an elevated level of PAP, heart failure, maternal death, maternal miscarriage, and premature delivery, which might be all due to the selective use by disease severity (Table 6). Even so, fetal growth restriction, fetal malformation, and newborn death were similar between patients treated with and without the use of prostaglandin. While the use of sildenafil seemed more frequent with maternal outcomes such as maternal death, miscarriage, and premature delivery, it appeared not to increase negative consequences such as fetal growth restriction, fetal malformation, and newborn death (Table 7). Of those who were administered diuretics, miscarriage was more frequent, but premature delivery and fetal outcomes such as fetal growth restriction, fetal malformation, and newborn death were not increased, although this was based on a small sample size (Table 8).

**Table 5.** Maternal and newborn outcomes of PAH-CHD patients by pulmonary artery pressure

| PAP (mmHg) | 25-49 (N=77) | | | 50-79 (N=16) | | | ≥ 80 (N=9) | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | N | %/Mean | SD | N | % | SD | N | % | SD | P |
| Maternal death | 2 | 0.03 | | 1 | 0.06 | | 0 | 0.00 | | 0.856 |
| Maternal pulmonary infection | 7 | 0.09 | | 5 | 0.31 | | 0 | 0.00 | | 0.249 |
| Maternal pulmonary embolism | 1 | 0.01 | | 0 | 0.00 | | 0 | 0.00 | | 0.685 |
| Preeclampsia | 5 | 0.06 | | 1 | 0.06 | | 0 | 0.00 | | 0.677 |
| Fetal growth restriction | 6 | 0.08 | | 3 | 0.19 | | 1 | 0.11 | | 0.812 |
| Postpartum hemorrhage | 2 | 0.03 | | 1 | 0.06 | | 0 | 0.00 | | 0.856 |
| Miscarriage | 10 | 0.12 | | 4 | 0.25 | | 3 | 0.33 | | <0.001 |
| Fetal malformation | 3 | 0.03 | | 1 | 0.06 | | 1 | 0.11 | | 0.491 |
| Premature delivery | 20 | 0.26 | | 7 | 0.44 | | 2 | 0.22 | | <0.0001 |
| Newborn death | 6 | 0.08 | | 1 | 0.06 | | 0 | 0.00 | | 0.419 |
| Newborn weight (g) | 60 | 2680 | 801 | 19 | 2441 | 741 | 2 | 2440 | 354 | 0.725 |
| Apgar score 1 minute | 60 | 7.56 | 2.67 | 19 | 7.21 | 2.35 | 2 | 7.50 | 0.71 | 0.131 |
| Apgar score 5 minute | 60 | 8.88 | 3.01 | 19 | 8.89 | 2.31 | 2 | 9.50 | 0.71 | 0.046 |

* Patients who delivered before 28 gestational weeks were excluded as abortion (n=21).

**Table 6.** Maternal and newborn outcomes of PAH-CHD patients by use of prostaglandin

| | No prostaglandin (N=70) | | | Used prostaglandin (N=32) | | | |
|---|---|---|---|---|---|---|---|
| | N | %/Mean | SD | N | %/Mean | SD | P |
| **NYHA classification** | | | | | | | |
| I-II | 55 | 0.79 | | 8 | 0.25 | | <0.001 |
| III-IV | 15 | 0.21 | | 24 | 0.75 | | |
| **PAP (mmHg)** | | | | | | | |
| 25-49 | 59 | 0.84 | | 11 | 0.34 | | <0.001 |
| 50-79 | 8 | 0.11 | | 15 | 0.47 | | |
| ≥80 | 3 | 0.04 | | 6 | 0.19 | | |
| **Heart Failure** | 6 | 0.09 | | 15 | 0.47 | | <0.0001 |
| **Patients' outcomes** | | | | | | | |
| Maternal death | 0 | 0.00 | | 3 | 0.09 | | 0.009 |
| Miscarriage | 12 | 0.17 | | 9 | 0.28 | | 0.007 |
| Premature delivery | 15 | 0.21 | | 14 | 0.44 | | 0.006 |
| Fetal growth restriction | 7 | 0.10 | | 3 | 0.09 | | 1.000 |
| Fetal malformation | 4 | 0.06 | | 1 | 0.03 | | 1.000 |
| Newborn death | 4 | 0.06 | | 3 | 0.09 | | 0.399 |
| Newborn weight (g) | 58 | 2784 | 736 | 23 | 2200 | 745 | 0.002 |
| Apgar score 1 minute | 58 | 7.85 | 2.36 | 23 | 6.52 | 2.84 | 0.034 |
| Apgar score 5 minute | 58 | 9.24 | 2.55 | 23 | 8.04 | 3.28 | 0.083 |

* Patients who delivered before 28 gestational weeks were excluded as abortion (n=21).

### Antithrombotic therapy

Antithrombotic use was related to the severity of disease, so patients with more likelihood of having heart failure were more often treated with antithrombotic medication. Therefore, premature delivery was higher (45%, 17/38) in individuals who used antithrombotic drug than those (19 %, 12/64) who did not use, probably due to the selective effect. We did not observe a marked difference in other maternal outcomes and fetal outcomes, as well as birth outcomes such as birth weight and Apgar score at 1 minute (Table 9).

**Table 7.** Maternal and newborn outcomes of PAH-CHD patients with or without using sildenafil

| | No sildenafil (N=80) | | | Used sildenafil (N=22) | | | |
|---|---|---|---|---|---|---|---|
| | N | %/Mean | SD | N | %/Mean | SD | P |
| **NYHA classification** | | | | | | | |
| I-II | 58 | 0.73 | | 5 | 0.23 | | <0.001 |
| III-IV | 22 | 0.28 | | 17 | 0.77 | | |
| **PAP (mmHg)** | | | | | | | |
| 25-49 | 62 | 0.78 | | 8 | 0.36 | | 0.001 |
| 50-79 | 14 | 0.18 | | 9 | 0.41 | | |
| ≥80 | 4 | 0.05 | | 5 | 0.23 | | |
| **Heart Failure** | 10 | 0.13 | | 11 | 0.50 | | <0.001 |
| **Patients' outcomes** | | | | | | | |
| Maternal death | 2 | 0.03 | | 1 | 0.05 | | 0.615 |
| Miscarriage | 12 | 0.15 | | 8 | 0.37 | | 0.012 |
| Premature delivery | 22 | 0.28 | | 7 | 0.32 | | 0.015 |
| Fetal growth restriction | 9 | 0.11 | | 1 | 0.05 | | 0.686 |
| Fetal malformation | 5 | 0.06 | | 0 | 0.00 | | 0.582 |
| Newborn death | 6 | 0.08 | | 1 | 0.05 | | 1.000 |
| Newborn weight (g) | 68 | 2667 | 795 | 13 | 2360 | 664 | 0.195 |
| Apgar score 1 minute | 68 | 7.65 | 2.57 | 13 | 6.54 | 2.37 | 0.150 |
| Apgar score 5 minute | 68 | 9.01 | 2.85 | 13 | 8.31 | 2.63 | 0.409 |

* Patients who delivered before 28 gestational weeks were excluded as abortion (n=21).

**Table 8.** Maternal and newborn outcomes of PAH-CHD patients by use of diuretics

| | No diuretics (N=63) | | | Used diuretics (N=39) | | | |
|---|---|---|---|---|---|---|---|
| | N | %/Mean | SD | N | %/Mean | SD | P |
| **NYHA classification** | | | | | | | |
| I-II | 50 | 0.79 | | 13 | 0.33 | | <0.001 |
| III-IV | 13 | 0.21 | | 26 | 0.67 | | |
| **PAP (mmHg)** | | | | | | | |
| 25-49 | 48 | 0.76 | | 22 | 0.56 | | 0.110 |
| 50-79 | 11 | 0.17 | | 12 | 0.31 | | |
| ≥80 | 4 | 0.06 | | 5 | 0.13 | | |
| **Heart failure** | 6 | 0.10 | | 15 | 0.38 | | <0.0001 |
| **Patients' outcomes** | | | | | | | |
| Maternal death | 0 | 0.00 | | 3 | 0.08 | | 0.025 |
| Miscarriage | 16 | 0.25 | | 5 | 0.13 | | 0.022 |
| Premature delivery | 12 | 0.19 | | 17 | 0.44 | | 0.023 |
| Fetal growth restriction | 6 | 0.10 | | 4 | 0.10 | | 1.000 |
| Fetal malformation | 3 | 0.05 | | 2 | 0.05 | | 1.000 |
| Newborn death | 3 | 0.05 | | 4 | 0.12 | | 0.446 |
| Newborn weight (g) | 47 | 2704 | 802 | 34 | 2500 | 745 | 0.248 |
| Apgar score 1 minute | 47 | 7.97 | 2.34 | 34 | 6.79 | 2.72 | 0.041 |
| Apgar score 5 minute | 47 | 9.3 | 2.47 | 34 | 8.35 | 3.18 | 0.136 |

* Patients who delivered before 28 gestational weeks were excluded as abortion (n=21).

## DISCUSSION

### Maternal outcome

This study examined treatment strategies and outcomes of pregnancy in 102 patients with pulmonary arterial hypertension managed at a single clinical hospital from 2009 to 2018. We found the mortality rate was 4.3%, that 20.59% of patients had heart failure, and 20.59% of then had an abortion before 28 gestational weeks. Despite a small sample size from a single clinical institution, the mortality was significantly lower than previously reported (13). Our study also supports the finding that maternal mortality associated with PAH-CHD has decreased over the last ten years, as previously reported (14). The three factors related to heart failure, NYHA functional class, and levels of PAP were associated with the risk of miscarriage and premature delivery. Higher NYHA functional class puts patients at a higher risk of having an underweight birth. This is consistent with the consensus that pregnant women who are NYHA functional class III-IV are at high risk for poor maternal and neonatal outcomes.

**Table 9.** Maternal and newborn outcomes of PAH-CHD patients by antithrombotic use

| | No antithrombotic therapy (N=64) | | | Used antithrombotic therapy (N=38) | | | |
|---|---|---|---|---|---|---|---|
| | N | %/Mean | SD | N | %/Mean | SD | P |
| **NYHA classification** | | | | | | | |
| I-II | 43 | 0.67 | | 20 | 0.53 | | 0.206 |
| III-IV | 21 | 0.33 | | 18 | 0.47 | | |
| **PAP (mmHg)** | | | | | | | |
| 25-49 | 46 | 0.72 | | 24 | 0.63 | | 0.190 |
| 50-79 | 11 | 0.17 | | 12 | 0.32 | | |
| ≥80 | 7 | 0.11 | | 2 | 0.05 | | |
| **Heart failure** | 10 | 0.16 | | 11 | 0.29 | | <0.001 |
| **Patients' outcomes** | | | | | | | |
| Maternal death | 2 | 0.03 | | 1 | 0.03 | | 1.000 |
| Miscarriage | 14 | 0.22 | | 7 | 0.18 | | 0.802 |
| Premature delivery | 12 | 0.19 | | 17 | 0.45 | | 0.007 |
| Fetal growth restriction | 5 | 0.08 | | 5 | 0.13 | | 0.292 |
| Fetal malformation | 2 | 0.03 | | 3 | 0.08 | | 0.358 |
| Newborn death | 3 | 0.05 | | 4 | 0.11 | | 0.420 |
| Newborn weight (g) | 50 | 2877 | 583 | 31 | 2611 | 480 | 0.379 |
| Apgar score 1 minute | 50 | 8.31 | 1.27 | 31 | 7.96 | 1.04 | 0.211 |
| Apgar score 5 minute | 50 | 9.77 | 0.56 | 31 | 9.77 | 0.51 | 0.922 |

**Fetal and birth outcome**

Because the use of various medication would have been due to the severity of disease at baseline, such as NYHA functional class or level of PAP, it is hard to evaluate any beneficial effects of medication on maternal outcomes, such as pregnant complications, maternal death, miscarriage, and premature delivery. However, our analysis showed that 1) fetal outcomes such as growth restriction, malformation, or newborn death were lower or at least not higher than those who did not use advanced therapy; 2) that patients who were administered diuretics had a lower rate of miscarriage than those who were not administered diuretics; and 3) The three classes of medications in the advanced therapy had a positive impact on birth outcome. Use of prostaglandin and sildenafil seemed to have infants with that both mean birth weight and Apgar score at 1 minute below normal or a healthy level, but women who had used diuretics tended to have babies with normal birth weight and good Apgar score at 1 minute, despite being patients with more severe symptoms of PAH.

**Antithrombotic benefits**

Antithrombotic treatment was associated with heart failure as well as with severe disease indicated by higher functional class and higher levels of PAP. Individuals who were administered antithrombotic therapy may have had a severe disease. Despite this, we observed that patients who used antithrombotic therapy had no difference in maternal, fetal, and birth outcomes except that premature delivery was higher in individuals who used antithrombotic treatment.

Since there is no standard anticoagulant therapy for pregnant women with PAH-CHD(15), patients without other thrombotic risk factors were administered a prophylactic dose (4000 IU QD) of low molecular weight heparin (LMWH). Patients with a high risk of thrombosis, including those with a history of thromboembolic events or atrial fibrilation, were administered a therapeutic dose of LMWH (4000 IU Q12 h) before delivery. Patients who took warfarin bef-ore and during pregnancy were switched to heparin ther-apy (0.5 mg/kg) 3 days before cesarean section. For these patients, heparin therapy was continued for three days after surgery, and warfarin treatment was restarted at 24 hours after surgery in the absence of high-risk factors for bleeding. The dosages were adjusted based on the international normalized ratio (INR). Because the risk of venous thromboembolism is 11-fold higher(16) in PAH patients than in healthy patients during the perinatal stage, anticoagulant therapy is strongly advocated(17).

LMWH does not cross the placental barrier, and thus is generally recommended for the treatment of pregnant women with PAH-CHD, with variable dosage. However, as postpartum hemorrhage can become a severe problem in PAH-CHD patients intensively treated with anticoagulants, the most effective and safest anticoagulant therapeutic strategy has not yet been identified(18, 19). In this study, one patient died of pulmonary thrombosis but did not receive any anticoagulant therapy; also, postpartum hemorrhage was only noted in three patients, two in non-heart failure and one in the heart failure. Although our study did not specify the type and extent of anticoagulant therapy used for pregnant patients with PAH-CHD, an appropriate balance must be achieved between bleeding and thrombotic risk.

**Oxytocin use**

Oxytocin did not increase the risk of heart failure in pregnant patients. Oxytocin was used after delivery to prevent postpartum hemorrhage in this sample of patients (81-86%), as it may reduce the risk of postpartum hemorrhage (20). It seemed likely that this use of oxytocin might be the reason that only three patients had a postpartum hemorrhage in this analysis. Most of the patients were administered with a low dose of oxytocin, 10 IU per day via intravenous drop for three days after delivery.

The usage of oxytocin in this post-partum interval might raise some concern because there have been reports that oxytocin can increase pulmonary vascular resistance and reduce systemic vascular resistance, leading to tachycardia, myocardial ischemia, and increased disease severity in women with PAH-CHD (21-23). Unfortunately, we were not able to collect the related data in this sample, although a published review indicated that high dose oxytocin might be more effective in preventing postpartum hemorrhage (20). Of note, in our study, three patients were diagnosed with postpartum hemorrhage, and none of them had received oxytocin therapy after delivery.

While the use of medication for PAH treatment has improved pregnancy outcomes of patients with PAH-CHD, particularly reduction in maternal deaths. The long-term survival benefits offered by these therapies have not yet been demonstrated (14, 24, 25). Because our data showed that medications were only used to treat patients with severe symptoms, the benefit of medications for all patients needs to be assessed with a larger sample size in a prospective study. There seemed to be no increase in the likelihood of adverse fetal outcomes such as restricted fetal growth or fetal malformations, but these impressions are based on a small sample. It is worth noting that individuals who used diuretics had a marked low frequency of miscarriage and had no difference in birth weight and Apgar score.

### Limitations

The observational study was for hypothesis generation and the results are only suggestive and need to be validated with formal studies. This study included all 102 PAH-CHD patients who had delivered at a single hospital from January 2008 to December 2018; therefore, biases cannot be ruled out. In retrospective descriptive analyses, confounding effects may not be avoidable. Therefore, there is a need for a larger prospective study. While we noted that medications might have some benefits on maternal, fetal, and birth outcomes, the fact that only patients with severe symptoms received medication may have reduced our ability to find a more significant impact of their use.

## CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest regarding the publication of this paper.

## REFERENCES


1. Task Force on the Management of Cardiovascular Diseases During Pregnancy of the European Society of C. Expert consensus document on the management of cardiovascular diseases during pregnancy. Eur Heart J. 2003;24(8):761-81.
2. D'Alto M, Mahadevan VS. Pulmonary arterial hypertension associated with congenital heart disease. European Respiratory Review. 2012;21(126):328-37.
3. Duffels MG, Engelfriet PM, Berger RM, van Loon RL, Hoendermis E, Vriend JW, et al. Pulmonary arterial hypertension in congenital heart disease: an epidemiologic perspe-ctive from a Dutch registry. Int J Cardiol. 2007; 120(2):198-204.
4. Engelfriet PM, Duffels MG, Moller T, Boersma E, Tijssen JG, Thaulow E, et al. Pulmonary arterial hypertension in adults born with a septal heart defect: the Euro Heart Survey on adult congenital heart disease. Heart. 2007;93(6):682-7.
5. Weiss BM, Zemp L, Seifert B, Hess OM. The outcome of pulmonary vascular disease in pregnancy: a systematic overview from 1978 through 1996. J Am Coll Cardiol. 1998; 31 (7): 1650-7.
6. Rubin LJ. Primary pulmonary hypertension. N Engl J Med. 1997;336(2):111-7.
7. Frost AE, Badesch DB, Barst RJ, Benza RL, Elliott CG, Farber HW, et al. The changing picture of patients with pulmonary arterial hypertension in the United States: how REVEAL differs from historic and non-US Contemporary Registries. Chest. 2011;139(1):128-37.
8. European Society of Gynecology, Association for European Paediatric Cardiology, German Society for Gender Medicine, Regitz-Zagrosek V, Bloms-trom Lundqvist C, Borghi C, et al. ESC Guidelines on the man-agement of cardiovascular diseases during pregnancy: the Task Force on the Management of Cardiovascular Dise-ases during Pregnancy of the European Society of Cardiology (ESC). Eur Heart J. 2011;32(24):3147-97.
9. Macchia A, Marchioli R, Marfisi R, Scarano M, Levantesi G, Tavazzi L, et al. A meta-analysis of trials of pulmonary hypertension: a clinical condition looking for drugs and research methodology. Am Heart J. 2007;153(6):1037-47.
10. McLaughlin VV, McGoon MD. Pulmonary arterial hypertension. Circulation. 2006;114(13):1417- 31.
11. Stewart R, Tuazon D, Olson G, Duarte AG. Pregnancy and primary pulmonaryhypertension: successful outcome with epoprostenol therapy. Chest. 2001;119(3):973-5.
12. Kraemer HC. A comment on "Beyond p-value: the rigor and power of study." Glob Clin Transl Res. 2020;2(1):7-9. DOI: 10.36316/gcatr.02.0022.
13. Bonnin M, Mercier FJ, Sitbon O, Roger-Christoph S, Jais X, Humbert M, et al. Severe pulmonary hypertension during pregnancy: mode of delivery and anesthetic management of 15 consecutive cases. Anesthesiology. 2005;102(6):1133-7; discussion 5A-6A.
14. Bedard E, Dimopoulos K, Gatzoulis MA. Has there been any progress made on pregnancy outcomes among women with pulmonary arterial hypertension? Eur Heart J. 2009; 30(3): 256-65.
15. Pitts JA, Crosby WM, Basta LL. Eisenmenger's syndrome in pregnancy: does heparin prophylaxis improve the maternal mortality rate? Am Heart J. 1977;93(3):321-6.
16. Khairy P, Ouyang DW, Fernandes SM, Lee-Parritz A, Economy KE, Landzberg MJ. Pregnancy outcomes in women with congenital heart disease. Circulation. 2006;113(4):517-24.
17. Curry RA, Fletcher C, Gelson E, Gatzoulis MA, Woolnough M, Richards N, et al. Pulmonary hypertension and pregnancy--a review of 12 pregnancies in nine women. BJOG. 2012; 119 (6):752-61.
18. McLaughlin VV, Archer SL, Badesch DB, Barst RJ, Farber HW, Lindner JR, et al. ACCF/AHA 2009 expert consensus document on pulmonary hypertension a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association developed in collaboration with the American College of Chest Physicians; American Thoracic Society, Inc.; and the Pulmonary Hypertension Association. J Am Coll Cardiol. 2009; 53(17):1573-619.
19. Duarte AG, Thomas S, Safdar Z, Torres F, Pacheco LD, Feldman J, et al. Management of pulmonary arterial hypertension during pregnancy: a retrospective, multicenter experience. Chest. 2013;143(5):1330-6.
20. Roach MK, Abramovici A, Tita AT. Dose and duration of oxytocin to prevent postpartum hemorrhage: a review. Am J Perinatol. 2013;30(7):523-8.

21. Price LC, Forrest P, Sodhi V, Adamson DL, Nelson-Piercy C, Lucey M, et al. Use of vasopressin after Caesarean section in idiopathic pulmonary arterial hypertension. Br J Anaesth. 2007;99(4):552-5.
22. Jonsson M, Hanson U, Lidell C, Norden-Lindeberg S. ST depression at the cesarean section and the relation to oxy-tocin dose. A randomized controlled trial. BJOG. 2010; 117 (1):76-83.
23. Svanstrom MC, Biber B, Hanes M, Johansson G, Naslund U, Balfors EM. Signs of myocardial ischemia after injection of oxytocin: a randomized, double-blind comparison of oxytocin and methylergometrine during Caesarean section. Br J Anaesth. 2008;100(5):683-9.
24. Rosenzweig EB, Kerstein D, Barst RJ. Long-term prostacyclin for pulmonary hypertension with associated congenital heart defects. Circulation. 1999;99(14):1858-65.
25. Galie N, Beghetti M, Gatzoulis MA, Granton J, Berger RM, Lauer A, et al. Bosentan therapy in patients with Eisen-menger syndrome: a multicenter, double-blind, randomized, placebo-controlled study. Circulation. 2006; 114(1) :48-54.



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