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Potential impact of specific therapy on pregnant women with pulmonary arterial hypertension without cardiac shunt: a descriptive study in northern China

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Abstract

Background: Pregnancy in women with pulmonary arterial hypertension (PAH) is a fatal condition, despite the effectiveness of PAH-specific therapies. The coverage status and effect of specific therapies in pregnant patients with PAH without cardiac shunts in China remain unclear. To investigate this issue, we conducted a multicenter retrospective study in northern China.

Methods: The study included 85 patients who were admitted to 4 clinical centers in Shandong Province between October 2010 and August 2020. Maternal endpoint events included (1) maternal death and/or (2) major adverse cardiac events, both occurring during pregnancy or within 6 weeks postpartum.

Results: Although the overall mortality rate was encouraging (11.8%), the number of patients receiving PAH-specific therapies was extremely low (28.2%). Moreover, only 15.3% of patients received adequate duration of PAH-specific therapy (≥4 weeks) before delivery, and this subgroup showed the lowest major adverse cardiac events rate (7.7%) compared with that in the untreated (19.7%) and short-time treated groups (<4 weeks; 54.5%).

Conclusion: Pregnant patients with PAH without cardiac shunts face significantly increased mortality risks. Short-term PAH-specific therapy does not guarantee favorable maternal outcomes. Prepregnancy screening, early identification, and timely intervention are expected to improve maternal outcomes in pregnant women with PAH.

Keywords: Major adverse cardiac events, Maternal mortality, Pregnancy outcome, Pulmonary arterial hypertension, Specific therapy

Introduction

Pulmonary arterial hypertension (PAH) is a debilitating disease characterized by progressive occlusive pulmonary vascular remodeling that eventually leads to right-sided heart failure and death. Pregnancy imposes additional risks for fatal complications in female patients with PAH, including rapid deterioration of right-sided heart function and maternal death, particularly during the late stages of gestation and the peripartum period.[1] Maternal death rates in patients with PAH can reach as high as 30% to 50%.[1,2] Consequently, pregnancy is strongly discouraged in patients with PAH as recommended by the 2015 and 2022 European Society of Cardiology/European Respiratory Society guidelines for pulmonary hypertension diagnosis and treatment.[3,4]

Despite these recommendations, the clinical management of pregnancy-associated PAH may be difficult for some special reasons. First, in certain countries or territories (including some underdeveloped regions in China), the rate of therapeutic abortion in pregnant patients with PAH remains low. This may be attributed to local traditional beliefs and/or health care resource limitations. For example, a retrospective investigation conducted by Luo et al.[5] that included 79 PAH-complicated pregnancies in southern China between 2004 and 2016 revealed that 72% of these patients continued their pregnancies, whereas only 23% opted for therapeutic abortion. Similarly, in a study conducted in southern India that included 73 women with pulmonary hypertension showed that more than 90% of these patients proceeded with delivery or cesarean section (C-section).[6] Second, PAH-associated pregnancies are sometimes inevitable as a significant number of cases remain symptomless, making the diagnosis of PAH challenging until cardiac function deteriorates during pregnancy.[7,8] Third, some early symptoms of PAH, such as moderate exertion dyspnea, chest pain, and peripheral edema, may be mistakenly interpreted as physiological consequences of pregnancy, leading to a delayed diagnosis of PAH.[7,8]

Contemporary PAH-specific drug therapy has greatly improved the prognosis of patients with general PAH.[9] Some of these drug classes, including phosphodiesterase type 5 inhibitors (PDE5is) and prostacyclin analogs (PGIs), can be administered to pregnant

The datasets generated during and/or analyzed during the current study are not publicly available due to privacy or ethical restrictions but are available from the corresponding author on reasonable request.

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women. However, currently, no data from prospective studies on the specific benefits of specific drug therapies on the clinical outcomes of pregnant women with PAH were obtained. In a recent study by Luo et al.,[5] an encouraging trend of decreased maternal mortality (approximately 15%) in pregnant patients with PAH was detected in comparison to previous data from developed countries (30% mortality) published a decade ago.[7,10–13] However, Luo et al.[5] reported a remarkably low rate of coverage of the specific drug therapy in these high-risk patients (30%); this starkly contrasts with the data obtained from developed countries (80%).[7,10–13] These results are paradoxical. It is important to note that patients in Luo and colleagues' cohort mainly had PAH associated with uncorrected congenital heart diseases, and whether the low coverage of the PAH-specific therapy worsened the outcomes in pregnant patients with PAH without cardiac shunts is unclear.

Based on this information, we conducted a multicenter retrospective study in northern China to clarify whether pregnant patients with PAH benefit from PAH-specific therapy.

Materials and methods

Data collection

This research was approved by the steering committee of Institutional Human Ethics Committee of Qilu Hospital (reference no. 2018-155) and was approved by the ethics committee at each participating center. Written informed consent was waived owing to the anonymized retrospective nature of the analysis. The medical records of pregnant women diagnosed with PAH were retrieved from 4 clinical centers: Qilu Hospital of Shandong University, Shandong Provincial Hospital Affiliated to Shandong First Medical University, Shandong Provincial Qianfoshan Hospital, and Affiliated Hospital of Qingdao University. This study included patients who were admitted for hospitalization between October 2010 and August 2020. The retrieved medical records were reviewed, and only group 1, patients with PAH without cardiac shunts, were included (idiopathic PAH, familial PAH, PAH associated with corrected congenital heart disease, and PAH associated with connective tissue diseases). All patients who received right-sided heart catheterization (RHC) (either before pregnancy or after parturition) and met the diagnostic criteria for PAH (mean pulmonary artery pressure of ≥25 mmHg and pulmonary artery wedge pressure of <15 mm Hg) were included. The exclusion criteria were as follows: (1) patients diagnosed by using only echocardiography without catheterization data; (2) group 1, PAH with uncorrected congenital heart diseases (including Eisenmenger syndrome) and vasoreactivity testing–positive idiopathic PAH; (3) group 2 (pulmonary hypertension due to left heart disease), group 3 (pulmonary hypertension due to lung diseases and/or hypoxia), or group 5, PAH (pulmonary hypertension with unclear, multifactorial mechanisms, or both) according to the 2015 European Society of Cardiology/European Respiratory Society guideline[3]; and (4) patients treated with therapeutic abortion within the first trimester. For each patient, we collected data on demographic characteristics, clinical history (including the history of specific drug therapy), World Health Organization functional class (WHO-FC), laboratory test data (including serum *N*-terminal pro B-type natriuretic peptide [NT-proBNP] level, hemoglobin level, and arterial partial pressure of oxygen [PaO_2]), and various echocardiography-derived parameters obtained before delivery (including systolic pulmonary artery pressure [sPAP], right ventricle [RV] diameter, and right atrial area [RAA]). The WHO-FC, NT-proBNP, and RAA were included in the baseline severity assessment. Patients with WHO-FC III/IV accompanied with either NT-proBNP of >1400 pg/mL or RAA of >26 cm^2 were defined as high-risk. Pulmonary arterial hypertension–specific therapy referred to PDE5i, PGIs, postpartum endothelin receptor antagonists, or a combination of them. Patients who received PAH-specific therapy before or after delivery were included in the treatment group; the remaining patients were assigned to the untreated group. Patients who received PAH-specific therapy ≥4 weeks before delivery were defined as long-treated, whereas those who received PAH-specific therapy for less than 4 weeks before delivery were defined as short-treated.

Endpoint assessment criteria

Maternal endpoint events included (1) maternal death and/or (2) major adverse cardiac events (MACEs), both occurring during pregnancy or within 6 weeks postpartum. Major adverse cardiac events included the deterioration of heart function (decline in WHO-FC, hypotension requiring vasopressors, and cardiac shock), de novo arrhythmia (sustained or nonsustained symptomatic arrhythmia), and cardiac arrest. The fetal/neonatal endpoint events included (1) the presence of neonatal asphyxia (Apgar score of ≤7) and/or (2) fetal or neonatal death.

Statistical analysis

Statistical analysis was performed using the SPSS software (version 13.0; Armonk, New York, NY, USA). Categorical data are presented as counts or percentages. Normal distribution was evaluated using the Kolmogorov-Smirnov test. Continuous variables were presented as mean with SD when distributed normally or as median with interquartile range. Categorical parameters were compared using Fisher exact test or Chi-squre test where appropriate. Continuous parameters were compared using Mann-Whitney U test or Kruskal-Wallis test where appropriate. Bonferroni test was carried out for post hoc analysis when necessary. Univariate and multivariate logistic regression analyses were used to identify clinical parameters associated with MACEs; parameters significant on the multivariate analysis were included in propensity score matching (PSM), which was used to control confounding factors. Paired patients were matched based on propensity scores using a standard caliper width of 0.15. Statistical comparisons between the propensity-matched samples were performed using the aforementioned methods. $P < 0.05$ was considered statistically significant.

Results

Baseline characteristics

The inclusion flowchart is shown in Fig. 1. The baseline characteristics and key clinical data of the 85 patients are summarized in Table 1. Only 24 patients received PAH-specific therapy. In all 85 patients, C-section was performed, with only 9.4% of which performed for therapeutic abortion. Compared with the untreated group, the treated group comprised older individuals (31 [26, 33] years vs. 27 [24, 31] years; $P = 0.029$) with higher sPAP (98 [78, 105] mm Hg vs. 73 [59, 88] mm Hg; $P < 0.001$) and larger RV diameter (32 [27, 37] mm vs. 28 [23, 33] mm; $P = 0.010$). Although no significant difference was detected, the treated group comprised a higher proportion of patients under general anesthesia and those classified as WHO-FC III/IV (worse cardiac FC). The 2 groups were comparable in PAH etiology composition, weeks of gestation upon delivery, percentage of nulliparous and de novo diagnosed PAH during pregnancy, NT-proBNP levels, and hemoglobin levels.

PAH-specific therapy not affecting overall maternal and fetal outcome

Patients in the treated group showed lower incidence of postpartum hemorrhage/thromboembolism (0.0% vs. 14.8%; $P = 0.042$); however, no significant difference was detected in the MACEs (19.7%

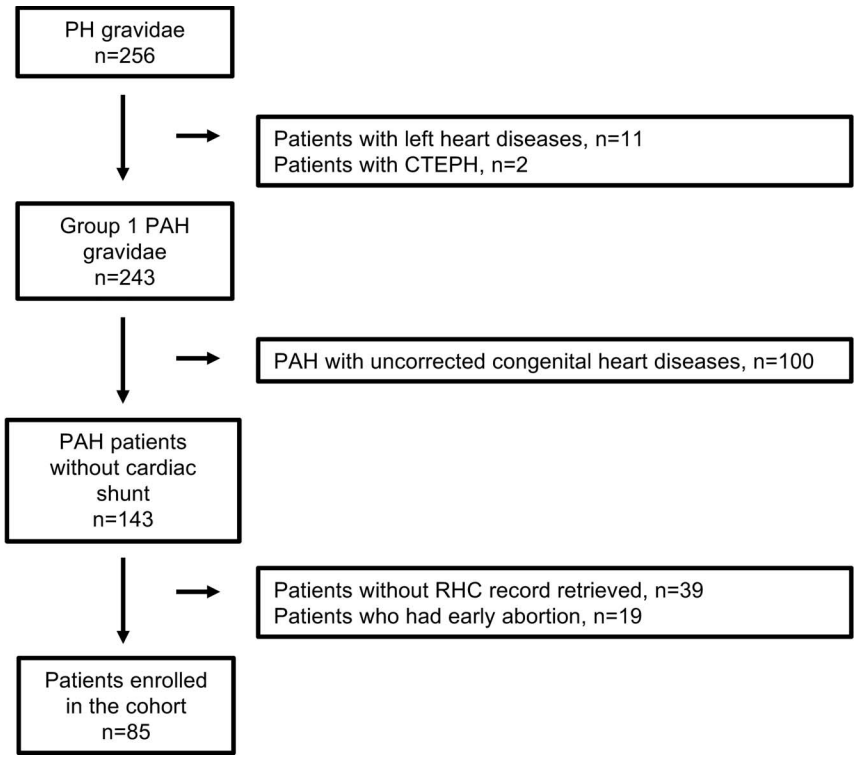

Figure 1. Study population and process of inclusion. CTEPH, chronic thromboembolic pulmonary hypertension; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; RHC, right-sided heart catheterization.

vs. 29.2%; P = 0.344) and mortality rates (9.8% vs. 16.7%; P = 0.458) between the untreated and treated groups. Contrary to expectations, the treated group exhibited increased MACEs and maternal death. Correlated with higher MACEs and mortality, the median duration of stay in the intensive care unit (4 [0, 5] days vs. 2 [0, 3] days; P = 0.002) and total hospitalization time (7 [5, 9] days vs. 14 [10, 19] days; P < 0.001) were significantly longer in the treated group than in the untreated group. No significant differences were observed in the proportion of therapeutic abortions, living deliveries, or fetal and neonatal outcomes between the 2 groups.

Moreover, we reported that patients in the treated group showed worse WHO-FC (WHO-FC III 45.9% vs. 69.7%; P = 0.085) and higher proportion of general anesthesia (13.1% vs. 29.2%; P = 0.081), which were proved to be factors associated with poor prognosis in PAH gravidae.[2,14,15] Moreover, the multivariate logistic regression showed that a history of general anesthesia, WHO-FC III/IV, and no history of PAH-specific therapy were independent risk factors for maternal MACEs (Supplemental Table 1, http://links.lww.com/ECCM/A75). Therefore, the covariates used in the propensity score calculation included age, history of general anesthesia, and WHO-FC III/IV. However, as shown in Supplemental Table 2 (http://links.lww.com/ECCM/A76), after baseline characteristics were matched using PSM method, the treated group did not show any improvement in either MACEs onset (25.0% vs. 29.2%; P = 0.745) or maternal death (12.5% vs. 16.7%; P = 0.683).

Beneficial effects of adequate duration of PAH-specific therapy on PAH gravidae

The duration of PAH-specific therapy varied considerably, which might have affected the conclusion. Given the negative results shown above, to further investigate the impact of therapy duration, a subgroup analysis was conducted. The analysis compared patients who received PAH-specific therapy for over 4 weeks (defined as the long-treated group; n = 13) before delivery with both untreated patients (defined as the untreated group; n = 61) and those treated for less than 4 weeks (defined as the short-treated group; n = 11). As shown in Table 2, the average duration of PAH-specific therapy before delivery was 102.2 days in the long-treated group compared with 2.5 days in the short-treated group. The frequencies of MACEs (7.7% vs. 19.7%) and maternal death (7.7 vs. 9.8%), although not significantly different, decreased in the long-treated group compared with those in the untreated group, with equal baseline characteristics. Post hoc analysis proved that the short-treated group had significantly higher frequencies of MACE than either untreated group (54.5% vs. 19.7%) or long-treated group (54.5% vs. 7.7%).

Furthermore, the short-treated group exhibited a higher proportion of newly diagnosed PAH (63.3% vs. 32.8%; P = 0.087), poorer WHO-FC (WHO-FC III/IV 90.9% vs. 45.9%; P = 0.075), and a higher rate of general anesthesia (45.5% vs. 13.1%; P = 0.0223), all of which were confounding factors. A PSM analysis was performed to compare the untreated and short-treated groups, as shown in Table 3. Results showed that treatment with PAH-specific drugs for less than 4 weeks did not show significant benefits in terms of maternal MACEs (54.5% vs. 63.6%) or death (27.3% vs. 36.4%).

Discussion

Our data from northern China revealed several key issues that may compromise the clinical outcomes in pregnant women diagnosed with PAH. First, the rate of elected therapeutic abortions was low (<10%). Therefore, the clinical management of these high-risk

Table 1

Demographic and Clinical Information of the Study Subjects Without and With PAH-Targeted Drug Therapy

	Untreated (n = 61)	Treated (n = 24)	*P*
Age, years	27 (24, 31)	31 (26, 33)	0.029
Weeks of gestation upon delivery	36 (34, 38)	34 (31, 37)	0.652
Nulliparous	32 (52.5%)	7 (29.2%)	0.071
PAH etiologies			0.383
Idiopathic PAH	18 (29.5%)	10 (41.7%)	
Postoperative CHD	29 (63.9%)	11 (45.8%)	
Connective tissue disease	1 (6.6%)	3 (12.5%)	
PAH diagnosed de novo during pregnancy	20 (32.8%)	12 (50.0%)	0.140
PAH specific drug therapy	N/A	24	—
PDE5i		20	
PGIs		10	
ERA after delivery		6	
Combined therapy		9	
General anesthesia	8 (13.1%)	7 (29.2%)	0.081
WHO-FC III/IV	28 (45.9%)	16 (66.7%)	0.112
NT-proBNP, pg/mL	367 (125, 807)	161 (93, 777)	0.271
Hemoglobin, g/L	112 (102, 124)	116 (104, 130)	0.397
sPAP, mmHg	73 (59, 88)	98 (78, 105)*	0.000
RAA, cm^2	21 (17, 24)*	28 (18, 34)	0.072
RV, mm	28 (23, 33)	32 (27, 37)	0.010
Pao_2, mmHg	79 (73, 112)*	83 (74, 91)*	0.353
Vasopressor and inotropic support after delivery	8 (13.1)	6 (25)	0.280
Days in ICU of survivors	2 (0, 3)	4 (0, 5)	0.002
Hospitalization days of survivors	7 (5, 9)	14 (10, 19)	0.000
MACEs	12 (19.7%)	7 (29.2%)	0.344
Deterioration of heart failure	7	7	—
De novo arrhythmia	3	0	—
Cardiac arrest	2	0	—
Maternal deaths	6 (9.8%)	4 (16.7%)	0.458
Postpartum hemorrhage/thromboembolism	9 (14.8%)	0 (0.0%)	0.042
Therapeutic abortions	6 (9.8%)	2 (8.3%)	0.597
Living deliveries	55 (90.2%)	22 (91.7%)	>0.999
Neonatal asphyxia	4 (4.7%)	1 (4.2%)	>0.999
Fetal deaths	3 (3.5%)	0 (0.0%)	0.555
Event-free subjects	35 (57.4%)	15 (62.5%)	0.806

Continuous data are expressed as median (lower quartile, upper quartile) and were compared using Mann-Whitney *U* test. Categorical data are expressed as n, n(%) were compared using Fisher exact test or Chi-square test where appropriate.

CHD, congenital heart disease; ERA, endothelin receptor antagonist; ICU, intensive care unit; MACEs, major adverse cardiac events; NT-proBNP, *N*-terminal pro B-type natriuretic peptide; PAH, pulmonary arterial hypertension; Pao_2, arterial partial pressure of oxygen; PDE5i, phosphodiesterase type 5 inhibitors; PGIs, prostacyclin analogs; RAA, right atrial area; RV, right ventricle; sPAP, systolic pulmonary artery pressure; WHO-FC, World Health Organization functional class.

*Some subjects had missing data in these items.

patients remains challenging in the obstetrics department. Evidence suggests that this problem is worldwide.[6,16,17]

Second, although both studies revealed low coverage of PAH-specific therapy, the overall mortality rate was higher in our study than that

Table 2

Comparing Long- and Short-Treated Cohorts Versus Untreated Cohorts

	Untreated (n = 61)	Short (n = 11)	Long (n = 13)	*P*
Age, years	27 (24, 31)	32 (30, 33)	30 (25, 34)	0.057
Weeks of gestation at delivery	36 (34, 38)	35 (33, 37)	32 (30, 37)	0.125
Newly diagnosed PAH	20 (32.8%)	7 (63.6%)	5 (38.5%)	0.151
WHO-FC III/IV	28 (45.9%)	10 (90.9%)	6 (46.2%)	0.021
NT-proBNP	367 (125, 807)	267 (101, 1038)	161 (91, 665)	0.569
RAA, cm^2	21 (16, 24)	28 (20, 36)	28 (15, 33)	0.159
High-risk stratum	19 (31.1%)	6 (54.5%)	6 (46.2%)	0.252
General anesthesia	8 (13.1%)	5 (45.5%)	2 (15.4%)	0.034
PAH-specific drug treatment duration before delivery, days	N/A	2.5 ± 5.8	102.2 ± 93.8	
Emergency cesarean section	5 (8.2%)	7 (63.6%)	1 (7.7%)	<0.001
MACEs	12 (19.7%)	6 (54.5%)	1 (7.7%)	0.015
Maternal death	6 (9.8%)	3 (27.3%)	1 (7.7%)	0.226

Continuous data are expressed as median (lower quartile, upper quartile) and were compared using Kruskal-Wallis test. Categorical data expressed as n (%) were compared using Fisher exact test or Chi-squre test where appropriate.

MACEs, major adverse cardiac events; NT-proBNP, *N*-terminal pro B-type natriuretic peptide; PAH, pulmonary arterial hypertension; RAA, right atrial area; WHO-FC, World Health Organization functional class.

Table 3

Comparisons Between Untreated and Treated Less Than 4 Weeks Cohorts After PSM

	Untreated (n = 11)	Short Treated (n = 11)
Age, years	26.4 ± 3.5	31.4 ± 3.6
NT-proBNP, pg/mL	4129 ± 6961	602 ± 755
General anesthesia	5 (45.5%)	5 (45.5%)
WHO-FC III/IV	10 (91%)	10 (91%)
MACEs	7 (63.6%)	6 (54.5%)
Maternal deaths	4 (36.4%)	3 (27.3%)

MACEs, major adverse cardiac events; NT-proBNP, *N*-terminal pro–B-type natriuretic peptide; PSM, propensity score matching; WHO-FC, World Health Organization functional class.

Data are n (%) or mean ± SD.

reported by Luo et al.[5] The patients included in the study by Luo et al.[5] primarily had PAH associated with uncorrected congenital heart disease, mostly with a systemic-to-pulmonary shunt, who well tolerated pregnancy even without PAH-specific drug treatment,[8] whereas in our study, patients with uncorrected congenital heart disease were excluded. Pregnancy imposes an extra risk on patients with PAH without cardiac shunts, and this special subgroup does not benefit from short-term PAH-specific treatment. Only those who had been treated with an adequate duration of PAH-specific therapy were at a lower risk of both MACEs and maternal death. This finding is consistent with the fact that while PDE5is result in significant pulmonary vasorelaxation and improve arterial oxygenation, the maximum effects are achieved after 60 minutes for sildenafil and 90 minutes for tadalafil.[18] It takes months for PAH-specific therapy to reduce pulmonary vascular resistance. The relatively short treatment duration contributes to the negative findings observed for PAH-specific therapy during pregnancy in China, not only in our study, but also in another Chinese center where the mortality remained as high as 30% even after receiving the PAH-specific treatment.[19] The conclusion is not restricted to our own cohort; however, it applies to published studies from the United Kingdom and the United States. However, it is important to acknowledge that both PDE5is and PGIs have demonstrated rapid hemodynamic changes in the pulmonary circulation. It should be noted that PAH-specific drugs were administered to patients with more severe hemodynamic conditions. The extent to which pregnant patients with PAH can benefit from the rapid and short-term PAH-specific therapies remains unclear.

As reported in North American and European studies, the mortality was as low as less than 5%.[16,20] Therefore, we still need to improve the efficacy of obstetric management in PAH-complicated pregnancies. Despite the low ratio of PAH-specific therapy for pregnant patients with PAH in China, the duration of therapy has been particularly short for Chinese patients, and the average treatment duration before delivery has been 15 weeks in China compared with the 27 weeks reported abroad.[16,20]

Third, in patients with PAH who choose to continue pregnancy, adequate PAH-specific therapy should be formulated, not only for a sufficiently long treatment duration, but also for more efficacious PAH-specific drugs. We reported only 10 patients receiving parenteral PGIs treatment and only 1 patient starting PGI injection 4 weeks before delivery. Whether the upfront combination of PDE5i and PGIs improves maternal outcomes requires further confirmation.

Although not statistically significant, the mean NT-proBNP level was much lower in the treated subgroup, and this subgroup was associated with poorer cardiac function (higher sPAP, larger RV diameter, and a higher incidence of WHO-FC III/IV). This discrepancy might be explained by the differential responsiveness of NT-proBNP to drug treatments compared with that of other cardiac function parameters. Multiple studies have revealed that NT-proBNP shows a faster response to PAH-specific therapies than that of other measurements of cardiac function (such as RV contractility and RV end-diastolic volume).[21–24] This phenomenon suggests that an adequate treatment duration of PAH-specific therapy may lead to better outcomes in patients with PAH during pregnancy.

Most importantly, the current study showed that a relatively low rate of awareness of PAH before pregnancy may delay the timely initiation of specific therapy. Our own data unveiled that in only 15% of the patients, the therapy was initiated at 4 weeks or earlier before delivery. Supporting this view, our data demonstrated that approximately 40% of the patients with PAH were diagnosed after pregnancy, and this is inconsistent with the reported figure in Europe, where greater than 75% of the PAH diagnoses are made before pregnancy.[16] This was more evident in the short-treated cohort, as shown in Table 2. The proportion of newly diagnosed PAH was as high as 63.6%, resulting in worse cardiac function, inadequate PAH-specific therapy, more emergency C-sections, and poor maternal outcomes. The PAH diagnosis was delayed possibly because of the nonspecific symptoms of PAH overlapping with normal pregnancy symptoms, such as dyspnea after exercise, fatigue, and peripheral edema. In the 4 centers involved in this study, echocardiography, the major method for PAH screening, was not used in routine antenatal examinations, which was another critical cause of the delayed diagnosis.

Given that PAH-associated pregnancies cannot be entirely avoided, it is essential to identify clinical strategies to improve pregnancy outcomes in patients with PAH, particularly in China and similar countries. Based on our data and those reported by others,[5] we propose the following recommendations: (1) avoid unnecessary delays in the diagnosis of PAH in pregnant women. These patients have a limited time window for initiating specific therapies to stabilize their disease condition. In fact, some of the delayed diagnoses of PAH are preventable. Currently, echocardiography is not mandatory in routine obstetric/antenatal examinations in China; thus, some early (nonspecific) symptoms of PAH may be ignored during such examinations in rural health care centers. Echocardiography and electrocardiography should be performed during routine examinations of patients with suspected symptoms. (2) Improve relevant education not only for patients, but also (probably more important) for their family members. Many patients have a strong desire to have children; however, they might have limited awareness of the risks associated with PAH-complicated pregnancies. In addition, decisions regarding pregnancy should not be solely influenced by family pressure, and patients should be well-informed to make correct choices. (3) Avoid unnecessary delays in initiating specific therapies. Based on our data, a particular treatment priority should be given to patients with de novo diagnosed PAH who are prone to increased risk and are associated with deteriorating disease conditions. Timely referral of potential high-risk patients to cardiologist/PAH specialist-staffed obstetric centers should be implemented. Providing additional education to primary obstetrics/gynecology practitioners may help in identifying and managing high-risk patients more effectively.

Limitations

First, a major limitation of the present study was the relatively small sample size, which was a common technical difficulty in similar studies owing to the low disease incidence. This precluded the conduction of a formal Cox regression analysis to objectively eliminate the effect of potential confounding factors (especially PAH severity) at baseline. Even after PSM, we could not completely exclude the possible influence of the severity in our negative finding on

pregnancy outcomes. Therefore, our study is largely descriptive and cannot precisely establish or nullify an independent causal relationship between the status of the specific therapy and the risk of maternal events. Future prospective studies with longer treatment durations and combined therapies may better define the benefits of the drugs in PAH-complicated pregnancies. Second, although all patients were diagnosed through RHC, it was performed years before pregnancy up to 2 years after delivery in de novo patients; this diversity makes it incomparable among patients at baseline. Therefore, RHC parameters were not included in the analysis. To date, several different risk assessment strategies have been widely used in clinical practice, all of which define WHO-FC III/IV and NT-proBNP of greater than 1400 ng/L as high-risk features for poor prognosis. Ultrasonic cardiogram–estimated sPAP or RV diameter was not correlated with prognosis; however, an RAA of less than 18 cm^2 is a low-risk feature, whereas an RAA of greater than 26 cm^2 is a high-risk feature according to the 2015 European Society of Cardiology/European Respiratory Society guidelines. It is unreasonable to use the 6-minute walking distance for risk stratification in pregnant women owing to the well-known movement restrictions during pregnancy. Thus, in this study, WHO-FC, NT-proBNP, and RAA were included in the baseline severity assessment instead of invasive hemodynamic parameters.

Conclusion

In summary, pregnant patients with PAH without cardiac shunts are at a much higher risk. Short-term PAH-specific therapy does not guarantee favorable maternal outcomes. Prepregnancy screening, early identification, and timely intervention are expected to further improve maternal outcomes in pregnant women with PAH.

Conflict of interest statement

The authors declare no conflict of interest.

Author contributions

Cui X was involved in study conceptualization, data curation and interpretation, and manuscript writing, revision, and final approval; Li M was involved in data collection and interpretation; Ji F was involved in data collection and interpretation; Feng H was involved in data interpretation and formal analyses; Li G was involved in data collection and interpretation; Ji Q was involved in data interpretation, data validation, formal analysis, and manuscript writing; Zhang H was involved in data collection, interpretation, and validation and formal analysis; Lu W was involved in study conceptualization, data collection, formal analysis, manuscript writing, and final approval.

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Ethical approval of studies and informed consent

The study followed the principles of the Declaration of Helsinki as revised in 2013. This research was approved by the steering committee of Institutional Human Ethics Committee of Qilu Hospital (reference no. 2018-155) and was approved by the ethics committee at each participating center. Written informed consent was waived owing to the anonymized retrospective nature of the analysis.

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References

[1] Olsson KM, Channick R. Pregnancy in pulmonary arterial hypertension. *Eur Respir Rev*. 2016;25(142):431–437. doi:10.1183/16000617.0079-2016
[2] Martin SR, Edwards A. Pulmonary hypertension and pregnancy. *Obstet Gynecol*. 2019;134(5):974–987. doi:10.1097/aog.0000000000003549
[3] Galiè N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension: the Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Heart J*. 2016;37(1):67–119. doi:10.1093/eurheartj/ehv317
[4] Humbert M, Kovacs G, Hoeper MM, et al. 2022 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Heart J*. 2022;43(38):3618–3731. doi:10.1093/eurheartj/ehac237
[5] Luo J, Shi H, Xu L, Su W, Li J. Pregnancy outcomes in patients with pulmonary arterial hypertension: a retrospective study. *Medicine*. 2020;99(23):e20285. doi:10.1097/md.0000000000020285
[6] Keepanasseril A, Pillai AA, Yavanasuriya J, Raj A, Satheesh S, Kundra P. Outcome of pregnancies in women with pulmonary hypertension: a single-centre experience from South India. *BJOG*. 2019;126(Suppl 4):43–49. doi:10.1111/1471-0528.15681
[7] Duarte AG, Thomas S, Safdar Z, et al. Management of pulmonary arterial hypertension during pregnancy: a retrospective, multicenter experience. *Chest*. 2013;143(5):1330–1336. doi:10.1378/chest.12-0528
[8] Li Q, Dimopoulos K, Liu T, et al. Peripartum outcomes in a large population of women with pulmonary arterial hypertension associated with congenital heart disease. *Eur J Prev Cardiol*. 2019;26(10):1067–1076. doi:10.1177/2047487318821246
[9] Bédard 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):256–265. doi:10.1093/eurheartj/ehn597
[10] Kiely DG, Condliffe R, Webster V, et al. Improved survival in pregnancy and pulmonary hypertension using a multiprofessional approach. *BJOG*. 2010;117(5):565–574. doi:10.1111/j.1471-0528.2009.02492.x
[11] Easterling TR, Ralph DD, Schmucker BC. Pulmonary hypertension in pregnancy: treatment with pulmonary vasodilators. *Obstet Gynecol*. 1999;93(4):494–498. doi:10.1016/s0029-7844(98)00524-9
[12] Curry RA, Fletcher C, Gelson E, et al. Pulmonary hypertension and pregnancy—a review of 12 pregnancies in nine women. *BJOG*. 2012;119(6):752–761. doi:10.1111/j.1471-0528.2012.03295.x
[13] McMillan E, Martin WL, Waugh J, et al. Management of pregnancy in women with pulmonary hypertension secondary to SLE and antiphospholipid syndrome. *Lupus*. 2002;11(6):392–398. doi:10.1191/0961203302lu216xx
[14] Pillutla P, Nguyen T, Markovic D, Canobbio M, Koos BJ, Aboulhosn JA. Cardiovascular and neonatal outcomes in pregnant women with high-risk congenital heart disease. *Am J Cardiol*. 2016;117(10):1672–1677. doi:10.1016/j.amjcard.2016.02.045
[15] Rex S, Devroe S. Anesthesia for pregnant women with pulmonary hypertension. *Curr Opin Anaesthesiol*. 2016;29(3):273–281. doi:10.1097/ACO.0000000000000310
[16] Sliwa K, van Hagen IM, Budts W, et al. Pulmonary hypertension and pregnancy outcomes: data from the Registry of Pregnancy and Cardiac Disease (ROPAC) of the European Society of Cardiology. *Eur J Heart Fail*. 2016;18(9):1119–1128. doi:10.1002/ejhf.594
[17] Dolgun ZN, Inan C, Sayin NC. Maternal and fetal outcomes in pregnancies with pulmonary hypertension: experience of a tertiary center. *Taiwan J Obstet Gynecol*. 2018;57(1):13–17. doi:10.1016/j.tjog.2017.10.032
[18] Ghofrani HA, Voswinckel R, Reichenberger F, et al. Differences in hemodynamic and oxygenation responses to three different phosphodiesterase-5 inhibitors in patients with pulmonary arterial hypertension: a randomized prospective study. *J Am Coll Cardiol*. 2004;44(7):1488–1496. doi:10.1016/j.jacc.2004.06.060
[19] Zhang J, Lu J, Zhou X, et al. Perioperative management of pregnant women with idiopathic pulmonary arterial hypertension: an observational case series study from China. *J Cardiothorac Vasc Anesth*. 2018;32(6):2547–2559. doi:10.1053/j.jvca.2018.01.043
[20] Thomas E, Yang J, Xu J, Lima FV, Stergiopoulos K. Pulmonary hypertension and pregnancy outcomes: insights from the National Inpatient Sample. *J Am Heart Assoc*. 2017;6(10):e006144. doi:10.1161/JAHA.117.006144

[21] Ghofrani HA, Galiè N, Grimminger F, et al. Riociguat for the treatment of pulmonary arterial hypertension. *N Engl J Med*. 2013;369(4):330–340. doi:10.1056/NEJMoa1209655
[22] Marra AM, Halank M, Benjamin N, et al. Right ventricular size and function under riociguat in pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension (the RIVER study). *Respir Res*. 2018;19(1):258. doi:10.1186/s12931-018-0957-y
[23] Vizza CD, Sastry BK, Safdar Z, et al. Efficacy of 1, 5, and 20 mg oral sildenafil in the treatment of adults with pulmonary arterial hypertension: a randomized, double-blind study with open-label extension. *BMC Pulm Med*. 2017;17(1):44. doi:10.1186/s12890-017-0374-x
[24] Lan WF, Deng Y, Wei B, et al. Echocardiographic evaluation of initial ambrisentan plus phosphodiesterase type 5 inhibitor on right ventricular pulmonary artery coupling in severe pulmonary arterial hypertension patients. *Front Cardiovasc Med*. 2022;9:843606. doi:10.3389/fcvm.2022.843606

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