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Maternal and Fetal Outcomes in Pregnant Women with Pulmonary Arterial Hypertension: A Single-Center Experience and Review of Current Literature

ORIGINAL INVESTIGATION

ABSTRACT

Background: Although pregnancy in women with pulmonary arterial hypertension has been considered a high-risk condition, current data regarding pregnancy with pulmonary arterial hypertension are scarce. In this study, we aimed to evaluate our single-center data on maternal and fetal outcomes in pregnant women with PAH and review currently available risk-based management strategies.

Methods: Our single-center study group comprised 35 women who became pregnant after the diagnosis of pulmonary arterial hypertension or in whom pulmonary arterial hypertension was diagnosed within early post-partum period. Clinical, laboratory, echocardiographic, and hemodynamic characteristics of pregnant and non-pregnant productive women with pulmonary arterial hypertension were compared, and similar comparison was also repeated for survivors and non-survivors in pregnant patient group.

Results: Pregnancy was noted in 15% of the 228 females with pulmonary arterial hypertension who were of hormonally productive ages, generally well-tolerated until delivery. Elective abortion and pre-term delivery were documented in 1 (2.8%) and 12 (35.3%) pregnant women, respectively. Switching to sildenafil was the standard medication during pregnancy. Cesarian section was the preferred method of delivery in all pregnant women with pulmonary arterial hypertension and was performed without any complication. Clinic deteoriation within the first week of delivery was observed in 5 (41.6%) patients. Maternal mortality was noted in 13 (37.1%) patients and was documented to cumulate within the first month of delivery. However, any sign predicting post-partum clinical deterioration was not found. No fetal mortality was observed.

Conclusion: Despite the development of advanced therapies, pregnancy in pulmonary arterial hypertension still carries a high mortality risk and requires multi-disciplinary expert center care with more proactive management strategies.

Keywords: Pulmonary arterial hypertension, mortality, pregnancy

Hacer Ceren Tokgöz [1]
Özgür Yaşar Akbal [1]
Ali Karagöz [1]
Barkın Kültürsay [1]
Seda Tanyeri [1]
Berhan Keskin [1]
Aykun Hakgör [2]
Şeyhmus Külahçıoğlu [1]
Zübeyde Bayram [1]
Süleyman Çağan Efe [1]
Cem Doğan [1]
İbrahim Halil Tanboğa [3]
Nihal Özdemir [1]
Cihangir Kaymaz [1]

[1]*Department of Cardiology, University of Health Sciences, Koşuyolu Heart Training and Research Hospital, İstanbul, Turkey*
[2]*Department of Cardiology, Faculty of Medicine, Medipol University, İstanbul, Turkey*
[3]*Department of Biostatistics, Faculty of Medicine, Nisantaşı University, İstanbul, Turkey*

Corresponding author:
Cihangir Kaymaz
✉ cihangirkaymaz2002@yahoo.com

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INTRODUCTION

Pulmonary arterial hypertension (PAH) has been considered a large spectrum of diseases due to different etiologies characterized by a progressive obstructive remodeling in distal pulmonary arteries, pressure burden on right ventricle and right atrium, right-sided heart failure, low-cardiac output, and impaired systemic arterial vasodilatory reserve.[1-7] The normal course of pregnancy is characterized by serial physiological changes including progressive increase in red blood cell mass, blood volume, stroke volume and cardiac output, decreases in hemoglobin level and total pulmonary vascular resistance, and initial small decrease and later increase in systolic and diastolic pressures.[8,9] The increase in cardiac output is mainly driven by 10%-15% increase in heart rate in the last trimester.[8,9] Although normalization in these physiological changes usually starts immediately after delivery, complete return to pregestational status may require up to 6 months.[8,9] The presence of severe PAH prior to gestation usually complicates the natural course of pregnancy.[8-17] Despite the development of advanced therapies, the severity of PAH, right ventricular failure, hypotension, and hypoxia have been

reported to increase the survival risk of fetus, while maternal mortality has been reported to cumulate in last days of gestation, especially during first weeks of postpartum period.[8-17]

In this study, our single-center experience on maternal and fetal outcomes in pregnant women with PAH was presented, and currently available risk-based management strategies were discussed.

METHODS

Our single-center study group comprised and retrospectively evaluated 35 women with PAH who became pregnant after the diagnosis of PAH or in whom PAH was diagnosed within post-partum period (up to 6 months after delivery).

The diagnostic algorithms, hemodynamic confirmation, and clinical sub-classification of pulmonary hypertension (PH) have been based on the recommendations of the European Society of Cardiology (ESC)/European Respiratory Society (ERS) 2015 PH Guidelines.[1] For hemodynamic definitions of PH on right heart catheterization, the mean pulmonary arterial pressure ≥ 25 mm Hg has been adopted, while pulmonary arterial wedge pressure ≤ 15 mm Hg and pulmonary vascular resistance > 3 Wood units criteria have also been included as a definition of pre-capillary PH.[1]

Reproductive age was defined as age between 18 and 49 years. Clinical etiologies responsible for PH, functional status, baseline risk scores as assessed by blood biochemistry, blood cell counts, echocardiographic and invasive hemodynamic measures of pulmonary circulation, and right heart functions of pregnant versus non-pregnant reproductive women with PAH were compared. Measures obtained immediately before delivery were utilized in pregnant PH group. Clinical deterioration was defined as increase in functional class during pregnancy and new-onset hemodynamic and respiratory instability with metabolic disturbances needing prolonged mechanical ventilation, parenteral inotropic, or inodilatory support, or extracorporeal membrane oxygenation (ECMO).

All female patients with PH who were regularly followed up have been informed regarding the high maternal risk of gestation and prohibition of pregnancy. A written informed consent was obtained from each patient, and the study protocol was reviewed and approved by the Institutional Ethics Committee. This study was conducted in accordance with the Declaration of Helsinki.

Statistical Methods

Continuous variables were represented as median and interquartile range (25th %-75th %), and categorical variables were represented as % and number. For group comparisons (pregnant or non-pregnant and death or alive), Mann–Whitney *U* test for continuous variables and the chi-square or Fisher's exact test for the categorical variables were utilized. A *P* value of <.05 was considered statistically significant. Primary endpoint was mortality within the first month and secondary endpoints were clinical worsening which needed mechanical ventilation (MV) or ECMO in the early postpartum period (7-10 days after delivery). All analyses were performed with R statistical software version 4.00 (Vienna, Austria).

RESULTS

In a single-center study as a part of EUPHRATES (Evaluation of Pulmonary hypertension rise factors associated with survival) registry overall 794 PAH ptients between January 2009 and December 2020, pregnancy was documented in 35 out of the 228 female patients with PAH who were in hormonally productive ages. Patient characteristics of pregnant women with PAH as compared to those in non-pregnant productive female patients with PAH were given in Table 1. Pregnant women had a younger age and a lower diastolic pressure versus non-pregnant women [27.9 (25.4-32.9) vs. 36.3 (28-43.5), $P < 0.001$ and 60 (59-70) vs. 70 (61-80), $P = 0.003$]. However, clinical etiologies of PH, functional status, blood biochemistry and cell counts, and echocardiographic and invasive hemodynamic measures of pulmonary circulation, and right heart functions were comparable (Table 1, 2). Mortality rates (%) of pregnant women were significantly higher compared to non-pregnant productive women ($P = .018$) (Figure 1).

Individual characteristics including age, PAH etiology, prior history, pregnancy course, delivery mode, anesthesiologic management, and post-delivery outcomes were summarized in Table 3. Moreover, calcium-channel blocker and targeted PAH therapies before and during pregnancy, and after delivery, and parenteral vasodilator or intropic agents provided during hospital follow-up were presented in Table 4. Sildenafil was the standard PAH treatment of choice during pregnancy period.[18] Elective abortion, small for gestational age (SGA), and pre-term delivery were noted in 1 (2.8%), 2 (5.7%), and 12 (35.3%) pregnant women, respectively. Cesarian section was the standard mode of delivery in all pregnant women with PAH and was performed without any complication. Clinical deteoriation within the first week of delivery was observed in 41.6% of patients with known PAH before pregnancy. Maternal mortality was noted in 13 out of the overall 35 pregnancies (37.1%). Comparison of the clinical, laboratory, echocardiographic, and invasive hemodynamic characteristics between survivors and non-survivors in the pregnant group with PH was presented in Table 5.

Maternal mortality was observed in 5 out of the 12 (41.6%) patients with diagnosis of PAH before pregnancy and

HIGHLIGHTS

- Women with pulmonary arterial hypertension should be informed about high mortality risks due to gestation and should be advised to avoid pregnancy.
- If pregnancy is unavoidable, multidisciplinary antenatal and postpartum care should be provided by an expert pulmonary hypertension/adult congenital heart disease center.
- Maternal cardiovascular complications occur in the early postpartum period even in the presence of a stable pregnancy and usually result in mortality. Therefore, close follow-up and proactive management strategies are essential.

Table 1. Comparison of Clinical, Laboratory, and Etiological Parameters Between Pregnant and Non-pregnant Reproductive Women with PH

	Pregnant (n = 35)	Non-pregnant Reproductive Women (n = 193)	*P*
Clinical variables			
Age (years)	27.9 (25.4-32.9)	36.3 (28-43.5)	<.001
Follow-up duration (days)	515 (181-951)	330 (62-1023)	.22
NYHA 1 (n, %)	-	4 (2)	.74
NYHA 2 (n, %)	7 (21.2)	31 (16)	
NYHA 3 (n, %)	17 (51.5)	106 (54.9)	
NYHA 4 (n, %)	11 (33.3)	52 (26.9)	
6-MWD (meter)	345 (186-380)	295 (151-360)	.29
Blood oxygen saturation (%)	95 (87.5-97)	93 (85-97)	.30
Heart rate (beats/min)	95.5 (75-104)	91 (81-102)	.96
Systolic blood pressure (mm Hg)	105 (92-120)	110 (100-122)	.15
Diastolic blood pressure (mm Hg)	60 (59-70)	70 (61-80)	.003
Labaratory variables			
NT-ProBNP (pg/mL)	411 (216-1300)	237 (73-622)	.03
Creatinine (mg/dL)	0.60 (0.50-0.719)	0.61 (0.56-0.70)	.46
Uric acid (mg/dL)	5.05 (4.63-6.47)	5.1 (4-6.3)	.64
D-dimer (ng/L)	0.49 (0.36-0.95)	0.46 (0.26-1.23)	.97
hs-Troponin (pg/mL)	0.02 (0.005-0.06)	0.006 (0.003-0.03)	.02
CRP (mg/L)	0.93 (0.34-4.71)	0.34 (0.31-1.33)	.047
Sodium (mEq/L)	139 (137-141)	138 (136-140)	.12
Potassium (mmol/L)	4.2 (3.95-4.4)	4.3 (4.1-4.53)	.14
Albumin (g/dL)	4.3 (3.95-4.6)	4.2 (3.70-4.60)	.43
White blood cell (per cubic mililiter)	8 (6.7-10.4)	7.70 (6.3-9.1)	.42
Hemoglobin (g/dL)	13.8 (11.3-14.6)	13.6 (12-15.3)	.22
Platelet (per cubic mililiter)	203 (168-268)	212 (169-278)	.81
Etiological variables			
Group 1			
IPAH (n, %)	18 (49)	55 (28)	.007
APAH-CTD (n, %)	1 (3)	7 (3.6)	.82
APAH-CHD (n, %)	12 (34)	98 (51)	.24
Large systemic-to-pulmonary shunt	1 (3)	12 (6)	.697
Eisenmenger	8 (23)	69 (36)	.138
Post-defect closure	3 (9)	19 (10)	.81
Group 2	0 (0)	2 (1)	NA
Group 3	0 (0)	6 (3)	NA
Group 4	0 (0)	18 (9)	NA
Group 5 (n, %) (sickle cell anemia)	1 (3)	3 (2)	.59
Segmental PAH (complex congenital heart disease)	3 (9)	29 (15)	.29
Mortality (n, %)	13 (37.1)	37 (19.1)	.018

6-MWD, 6-minute walk distance; IPAH, idiopathic pulmonary arterial hypertension; ASD, atrial septal defect; VSD, ventricular septal defect; PDA, patent ductus arteriosus; APAH-CHD, congenital heart disease-associated pulmonary arterial hypertension; CTD, connective tissue disease; APAH-CTD, connective tissue disease-associated pulmonary arterial hypertension; NYHA, New York Heart Association.

occurred within the first month following the delivery but not in 22 patients without any PAH diagnosis before gestation. Small gestational age was corrected by percentile curves developed for preterm delivery. No fetal mortality was observed. However, there was no pre- or peripartum sign predicting the post-partum clinical deterioration and lethal course. Pre-, peri-, and immediate post-partum measures were comparable between recovered and dead patients. These sudden-onset clinical worsening episodes are characterized by rapidly progressive systemic oxygen desaturation and circulatory failure and resulted in death despite the advanced PAH management strategies. Intravenous iloprost added as background sildenafil therapy which was maintained during pregnancy period and endothelin receptor

Table 2. Comparison of the Echocardiographic and Invasive Hemodynamic Characteristics Between Pregnant Women with PH and Non-pregnant Productive Women with PH

	Pregnant (n = 35)	Non-pregnant Reproductive Woman (n = 193)	*P*
Echocardiographic variables			
Eccentricity index > 1.1 (n, %)	28 (80)	143 (74)	.94
IAS bulging (n, %)	7 (20)	42 (22)	.94
Tricuspid max velocity (m/s)	4.55 (3.95-5.10)	4.4 (3.9-4.95)	.31
Tricuspid max gradient (mm Hg)	83 (69-105)	80 (60-95)	.17
Tricuspid mean gradient (mm Hg)	55 (46-70)	50 (40.5-63.5)	.15
Right atrial pressure (mm Hg)	8 (5-10)	10 (5-10)	.41
Right atrial area (centimeter square)	17.3 (14-23.1)	20 (16-22.7)	.40
Pulmonary artery diameter (centimeter)	3.5 (3-3.90)	3.2 (2.8-3.7)	.21
TAPSE (centimeter)	1.75 (1.6-2.08)	2 (1.58-2.2)	.18
TDI St (cm/s)	12 (10-13)	12 (9.95-14)	.62
Inferior vena cava diameter (centimeter)	1.9 (1.55-2.05)	1.80 (1.50-2.0)	.69
Presence of inferior cava plethore [n, (%)]	5 (14.3)	36 (18.7)	
Ejection fraction (%)	64 ± 3.39	64.7 ± 1.18	.19
Catheterization variables			
Aortic systolic pressure (mm Hg)	120 (104-130)	122 (112-137)	.13
Aortic diastolic pressure (mm Hg)	70 (64.5-80)	70 (62-77)	.28
Aortic mean pressure (mm Hg)	90 (79.8-96.3)	90 (82-100)	.50
LVEDP/PCWP (mm Hg)	10 (8-12)	11.5 (8.25-14)	.08
Pulmonary artery systolic pressure (mm Hg)	96 (76-116)	96 (65-119)	.41
Pulmonary artery diastolic pressure (mm Hg)	44.5 (32.5-53)	37 (25-58)	.32
Pulmonary artery mean pressure (mm Hg)	63 (50-72)	60 (41-81)	.58
Cardiac output (L/min)	3.84 (3-4.6)	4 (3.4-5)	.26
Cardiac index (L/min/m^2)	2.2 (2-2.8)	2.5 (2.1-3)	.35
Trans-pulmonary gradient (mm Hg)	55 (41-65)	46 (27-67)	.24
Right atrial pressure (mm Hg)	7 (5-10)	8 (5-11)	.58
Trans-systemic gradient (mm Hg)	83 (75.5-90.5)	82 (73-90)	.43
Diastolic pulmonary gradient (mm Hg)	32 (20-40)	25.5 (12-43)	.3
Pulmonary vascular resistance (Woods unit)	11 (8.3-14.8)	10 (5.5-15.1)	.49
Systemic vascular resistance (Woods unit)	21.1 (17.4-23.8)	20 (16-25)	.56
PVR/SVR ratio	0.52 (0.40-0.67)	0.48 (0.30-0.74)	.89
SVO_2 (%)	67 (53-70)	64 (57-70)	.506

Plethore was defined as inferior cava diameter >21 mm with decreased inspiratory collapse (<50% with a sniff or <20% with quiet inspiration).
IAS, interatrial septum; PVR/SVR, pulmonary vascular resistance/systemic vascular resistance ratio; LVEDP, left ventricular end-diastolic pressure; PCWP, pulmonary capillary wedge pressure; TAPSE, tricuspid annular plane systolic excursion; TDI St, tissue Doppler imaging peak systolic tricuspid annular velocity; n, number.

antagonists initiated in post-partum period were standard advanced PAH therapies after delivery, and inhaled nitric oxide instead of sildenafil was preferred in cases of prolonged MV. Mechanical ventilation and ECMO were needed in 4 patients. However, none of these patients recovered after treatment using ECMO. In 1 patient who was admitted to our hospital with severe PAH following the second day of delivery in another hospital, urgent bilateral lung transplantation (tx) on the 110th day of the waiting period with intensive care was done. The patient was followed up with intravenous iloprost and noradrenaline without needing MV, and cardiac catheterization was performed on the 10th day of hospitalization. Oral bosentan and tadalafil were added to her therapy after catheterization (Table 3). Her functional status was functional class (FC) 4 despite triple combination of PAH therapy and was added to the urgent lung transplant list by decision of PH team council. This patient was discharged from the hospital on 40th day of the operation and is still asymptomatic in the second year of post-transplant follow-up period. After transplantation, she continued to take bosentan and tadalafil with immunosuppressive therapy (tacrolimus, prednisolone), and rivaroxaban was added to therapy because of thrombosis in lower extremity arteries and veins after transplantation. This PAH-targeted therapy seemed to contribute to reverse remodeling of right ventricle in the post-transplantation period. Duration of bosentan and tadalafil therapy was decided to maintain until a final control new cardiac catheterization. N-terminal pro-brain natriuretic peptide (Nt-proBNP), FC, 6-minute walking distance, and echocardiogram measures improved significantly.

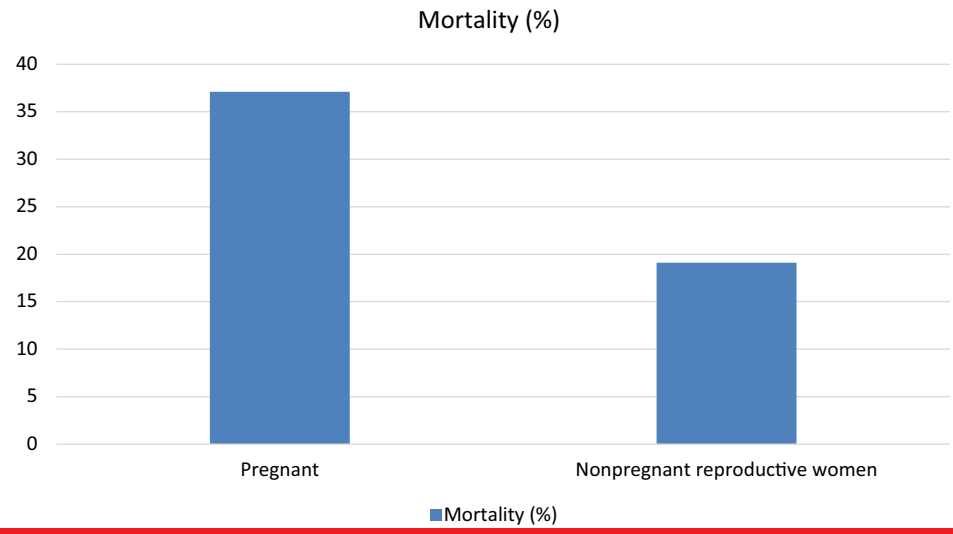

Figure 1. Mortality rates (%) of pregnant and non-pregnant women with PAH. PAH, pulmonary arterial hypertension.

DISCUSSION

Maternal and fetal outcomes in 35 pregnant women with PAH in our single-center study seem to be consistent with those reported in the currently available literature. The mortality was significantly higher in women with PAH diagnosed before, during, or after pregnancy as compared to fertile women without pregnancy after the diagnosis of PAH. None of our patients with PAH experienced maternal problem during their pregnancy periods. The overall maternal mortality rate was 37.1% and this rate rose to 41.6% in women with known PAH before pregnancy and was documented to be cumulated within the first month of delivery. All postpartum maternal deaths were observed in patients with the diagnosis of PAH before pregnancy or while pregnant. In women admitted to our hospital during the postpartum period, the history of PAH before pregnancy remains unclear. However, post-partum clinical deterioration and mortality remained unpredictable. No fetal mortality was noted.

Maternal mortality risk in severe PAH or Eisenmenger syndrome (ES) has been reported to vary between 30% and 50% in older series and has ranged from 17% to 33% in more recent series.[1,7-27] More importantly, in accordance with our results, maternal mortality occurs even in patients with little or no disability before or during pregnancy.[7-27] Late hospitalization, severity of PH, and utilization of general anesthesia have been reported as risk factors for maternal mortality.[1,7-28] Neonatal survival rates ranged from 87% to 89% in the offspring of pregnant PH patients.[7-17] Cyanosis poses a significant risk to the fetus, and a live birth is unlikely if oxygen saturation (sat % O_2) < 85%.[7-17]

Several risk models including modified World Health Organization classification, Cardiac Disease in Pregnancy (CARPREG), CARPREG II, and the Zwangerschap bij Aangeboren HARtAfwijking [Pregnancy in Women With Congenital Heart Disease] weighted risk score have been developed to stratify maternal cardiac risk in women with various cardiovascular diseases including PH and related pathologies who become pregnant.[7-13] The first CARPREG risk score consists of 4 predictors and there was no specific definition addressing any form of PH.[11] Novel risk score of CARPREG II has been based on 10 independent predictors of maternal cardiac risk including 4 criteria derived or modified from first CARPREG score and 6 newly defined risk predictors.[12] Although gestational period in patients with PAH was associated with the lowest frequency of complications, the risks for cardiac events have been reported to rise in the first postpartum week and did not fully resolve until the sixth post-partum month. When comparing the period between 1994 and 2000 and the period between 2001 and 2014, the overall rates of cardiac complications during pregnancy have not changed.[12] American College of Cardiology (ACC) and American Heart Association (AHA) 2018 Guidelines for the Management of Adults With Congenital Heart Disease (ACHD) highlighted a new classification to cover the complexity of anatomy (A) and physiological stage (P), which are not always correlated.[7] Pregnant women may move from one ACHD AP classification to another over time.[7]

European Registry of Pregnancy and Cardiac Disease (ROPAC) is an ongoing worldwide registry that includes pregnant women with congenital or structural cardiac diseases.[10,14,21] An interim analysis documented PH in 151 (5%) out of the 2966 pregnancies evaluated in ROPAC population.[14] In more than 75% of patients, PH was diagnosed before gestation, and PAH accounted for 26% of the overall pregnancies with PH.[14] The PAH associated with postoperative ACHD was the most prevalent subgroup (10%), and idiopathic PAH, ES, prevalent systemic to pulmonary shunts, and other PAH were noted in 3%-5% of the pregnant with PH.[14] Premature delivery, low-birth weight, miscarriages, fetal mortality, and neonatal mortality were documented in 24.7%, 19%, 6.6%, 2%, and 0.7%, respectively.[14] Except for the low birth weight that was more frequent in other PAH and ACHD-PAH groups, fetal and neonatal outcomes were compared among the clinical PH groups. Cesarian delivery was noted in 63.4% of these pregnancies and general anesthesia was utilized in one-third of these procedures. Antithrombotic medications were reported in 22.5% of the PH pregnancies.[14] This risk of mortality tended to be

Table 3. Summary of Individual Characteristics, Delivery Mode, Anesthesiologic Management, and Post-delivery Course in Pregnant Women with PH

Patient	Age (Year)	Diagnosis	Time of PAH Diagnosis	Number of Prior Pregnancy (TnAnLn)	Mode of Delivery	Anesthesia	Obstetric Complications	Gestational Age (Week)	Neonatal Complications	Mortality	Mortality Time in the First Month (Day)	Cause of Mortality	Time of Clinical Worsening (Day)	Type of In-hospital Support
1	32	APAH-post-defect closure	After pregnancy	T3A1L2	C/S	General	No	38	No	No	-	-	-	-
2	31	IPAH	While pregnant	T2A0L2	C/S	General	Preterm labor	34	Preterm, SGA	Yes	17	Hipoxia, right heart failure	1	Inotropes, MV, ECMO
3	24	IPAH	Before pregnancy	T3A2L1	C/S	General	Preterm labor	35	Preterm	No	-	-	-	-
4	23	IPAH	After pregnancy	T1A0L1	VD	No	No	38	No	Yes	26	Hipoxia, right heart failure	1	Inotropes, MV
5	30	IPAH	After Pregnancy	T2A0L2	C/S	General	No	38	No	No	-	-	-	-
6	31	IPAH	After pregnancy	T1A0L1	VD	No	Preterm labor	36	Preterm	No	-	-	-	-
7	38	IPAH	Before pregnancy	T2A1L1	TA	Sedation	-	8	Abort	-	-	-	-	-
8	33	IPAH	After pregnancy	T1A0L1	C/S	General	No	38	No	Yes*	-	-	-	-
9	35	IPAH	After pregnancy	T2A0L2	C/S	General	No	37	No	No	-	-	-	-
10	26	IPAH	While pregnant	T2A1L1	C/S	General	Preterm labor	36	Preterm	Yes	17	Hipoxia, right heart failure	1	
11	29	IPAH	After pregnancy	T1A0L1	C/S	General	No	38	No	No	-	-	-	-
12	28	Eisenmenger	Before pregnancy	T1A0L1	C/S	General	No	39	No	Yes	37	SVA	3	MV
13	26	Segmental PAH (complex congenital)	Before pregnancy	T1A0L1	C/S	General	Preterm labor	28	Preterm	Yes*	-	-	-	-
14	28	Segmental PAH (complex congenital)	Before pregnancy	T1A0L1	C/S	General	Preterm labor	36	Preterm	No	-	-	-	-
15	34	IPAH	After pregnancy	T2A0L2	C/S	General	No	39	No	No	-	-	-	-
16	31	IPAH	After pregnancy	T1A0L1	C/S	General	No	37	No	Yes*	-	-	-	-
17	28	APAH-post-defect closure	After pregnancy	T1A0L1	C/S	General	No	38	No	Yes*	-	-	-	-
18	27	Eisenmenger	After pregnancy	T1A0L1	C/S	General	Preterm labor	26	Preterm	No	-	-	-	-

(*Continued*)

Table 3. Summary of Individual Characteristics, Delivery Mode, Anesthesiologic Management, and Post-delivery Course in Pregnant Women with PH (*Continued*)

Patient	Age (Year)	Diagnosis	Time of PAH Diagnosis	Number of Prior Pregnancy (TnAnLn)	Mode of Delivery	Anesthesia	Obstetric Complications	Gestational Age (Week)	Neonatal Complications	Mortality	Mortality Time in the First Month (Day)	Cause of Mortality	Time of Clinical Worsening (Day)	Type of In-hospital Support
19	24	IPAH	Before pregnancy	T1A0L1	C/S	General	Preterm labor	34	Preterm	No	-	-	-	-
20	24	Eisenmenger	After pregnancy	T1A0L1	C/S	General	No	38	No	No	-	-	-	-
21	35	IPAH	After pregnancy	T2A1L1	C/S	General	Preterm labor	34	Preterm	No	-	-	-	-
22	26	APAH-post-defect closure	After pregnancy	T1A0L1	C/S	General	No	39	No	No	-	-	-	-
23	36	Eisenmenger	After pregnancy	T5A0L5	VD	No	No	39	No	Yes*	-	-	-	-
24	28	Eisenmenger	After pregnancy	T3A0L3	VD	No	No	38	No	No	-	-	-	-
25	34	IPAH	After pregnancy	T1A0L1	VD	No	No	39	No	No	-	-	-	-
26	24	Group 5 (sickle cell anemia)	After pregnancy	T1A0L1	VD	No	No	38	No	Yes*	-	-	-	-
27	30	IPAH	Before pregnancy	T1A0L1	C/S	General	Preterm labor	36	Preterm	No	-	-	-	-
28	21	IPAH	After pregnancy	T1A0L1	VD	No	No	38	No	Yes*	-	-	-	-
29	20	Eisenmenger	Before pregnancy	T2A1L1	C/S	General	Preterm labor	33	Preterm, SGA	No	-	-	-	-
30	25	Segmental PAH (complex congenital)	Before pregnancy	T2A0L2	C/S	General	No	38	No	Yes	13	Hipoxia, right heart failure	1	Inotropes, MV, ECMO
31	27	Large syste mic-to-pul monary shunt-APAH	Before pregnancy	T1A0L1	C/S	General	No	39	No	Yes	13	Hipoxia, right heart failure	1	Inotropes, MV, ECMO
32	27	APAH-CTD	After pregnancy	T2A0L2	C/S	General	Preterm labor	36	Preterm	No	-	-	-	-
33	25	Eisenmenger	Before pregnancy	T2A0L2	C/S	General	No	37	No	No	-	-	-	-
34	19	Eisenmenger	After pregnancy	T1A0L1	C/S	General	No	42	No	No	-	-	-	-
35	23	IPAH	After pregnancy	T1A0L1	VD	No	No	39	No	No	-	-	-	-

*In those who did not die in the first month, there is long-term mortality unrelated to pregnancy.
C/S, cesarean section; TA, therapeutic abortus; TnAnLn, total number of pregnancy, number of abortions, number of live birth; VD, vaginal delivery; ECMO, extracorporeal membrane oxygenation; MC, mechanical ventilation; IPAH, idiopathic pulmonary arterial hypertension; SGA, small for gestational age; APAH-CTD, connective tissue disease-associated pulmonary arterial hypertension.

Table 4. Summary of Medications, Clinical, Echocardiographic, and Hemodynamic Parameters in Pregnant Women with PH

Patient	Diagnosis	Time of PAH Diagnosis	Drugs Before Pregnancy	Drugs During Pregnancy	Drugs After Pregnancy	In-hospital Post-partum Medications	PASP (mm Hg)	PAMP (mm Hg)	PVR (WU)	CI (L/min/m²)	FC[c]	6-MWD[c] (m)	BNP/ Nt-ProBNP[c] ng/L	TR Vmax[c] m/s	Tapse[c] (cm)	FC[d]	6-MWD[d] (m)	BNP/ Nt-ProBNP[d] (ng/L)	TR Vmax[d] (m/s)	Tapse[d] (cm)
1	APAH-post-defect closure	After pregnancy	0	0	MAS+TAD+ SEL	-	102	69	11	3.1	-	-	-	-	-	4	50	487	5.3	1.9
2	IPAH	While pregnant	0	0	0	IV Iloprost, NE	85	57	9		4	2	134	4.8	2.1	-	-	-	-	-
3	IPAH	Before pregnancy	MAS+TAD	SIL	MAS+TAD+ SEL	Inhaled NO, NE, Milrinon	95	58	10	2.8	3	250	184	4.5	1.9	4	15	679	5	2
4	IPAH	After pregnancy	0	0	MAS + TAD	-	97	63	17.58	1.7	-	-	-	-	-	4	50	1225	4.3	1.6
5	IPAH	After pregnancy	0	0	MAS + TAD	-	110	71	-	-	-	-	-	-	-	3	360	311	4.7	-
6	IPAH	After pregnancy	0	0	MAS + TAD	-	140	85	-	-	-	-	-	-	-	3	425	334	3.9	1,.8
7	IPAH	Before pregnancy	MAS+TAD	MAS+TAD	MAS+TAD	-	140	85	-	-	3	360	208	4.8	2.2	-	-	-	--	-
8	IPAH	After pregnancy	0	0	AMB+TAD	-	60	40	11.1	1.5	-	-	-	-	-	4	30	7314	4.4	1.5
9	IPAH	After pregnancy	0	0	MAS+TAD	-	116	69	22	1.9	-	-	-	-	-	3	180	2913	5.6	1.6
10	IPAH	While pregnant	0	SIL+ILO	MAS+SIL+ILO	IV Iloprost, NE	-	-	-	-	4	15		5	2.2	-	-	-	-	-
11	IPAH	After pregnancy	0	0	MAS+TAD	-	60	34	5.7	2.5	-	-	-	-	-	3	400	20	3.5	-
12	Eisenmenger	Before pregnancy	BOS+SIL	SIL	BOS+SIL	IV Iloprost	169	97	-	-	3	420	-	4.7	2.2	-	-	-	-	-
13	Segmental PAH (complex congenital)	Before pregnancy	BOS	BOS[a]	BOS	IV Iloprost	125	80	-	-	3	350	123	-	-	-	-	-	-	-
14	Segmental PAH (complex congenital)	Before pregnancy	MAS+TAD	SIL	MAS+TAD	IV Iloprost	125	77	-	-	2	510	126	5.5	3.4	4	-	-	-	-
15	IPAH	After pregnancy	0	0	BOS	-	115	70	19.6	1.8	-	-	-	-	-	4	100	376	4.3	1.3
16	IPAH	After pregnancy	0	0	BOS+SIL	-	76	46	8.7	2.54	-	-	-	-	-	4	150	-	5	1.2
17	APAH-post-defect closure	After pregnancy	0	0	MAS+TAD	-	72	51	7.3	3.1	-	-	-	-	-	4	100	5904	4.1	1.9
18	Eisenmenger	After pregnancy	0	0	MAS+TAD	-	115	72	19	2.1	-	-	-	-	-	4	10	238	5.7	1.6
19	IPAH	Before pregnancy	SIL	SIL	MAS+SIL	IV Iloprost	51	35	3.5	3.3	2	430	-	3.2	2	3	385	148	3.5	2.4
20	Eisenmenger	After pregnancy	0	0	MAS+TAD	-	94	72	12.7	2	-	-	-	-	-	3	380	1300	4.1	1.6
21	IPAH	After pregnancy	0	0	MAS	-	103	63	15	2.1	-	-	-	-	-	3	356	75	3.9	203
22	APAH-post-defect closure	After pregnancy	0	0	MAS	-	73	44	9.5	2.3	-	-	-	-	-	3	285	209	3.5	1.6
23	Eisenmenger	After pregnancy	0	0	MAS+TAD	-	135	88	17	2.8	-	-	-	-	-	3	365	250	5.1	1.3
24	Eisenmenger	After pregnancy	0	0	MAS	-	80	49	3.5	3	-	-	-	-	-	3	340	1713	3.7	1.3

(*Continued*)

Table 4. Summary of Medications, Clinical, Echocardiographic, and Hemodynamic Parameters in Pregnant Women with PH (*Continued*)

Patient	Diagnosis	Time of PAH Diagnosis	Drugs Before Pregnancy	Drugs During Pregnancy	Drugs After Pregnancy	In-hospital Post-partum Medications	PASP (mm Hg)	PAMP (mm Hg)	PVR (WU)	CI (L/min/m²)	FC[c]	6-MWD[c] (m)	BNP/ Nt-ProBNP[c] ng/L	TR Vmax[c] m/s	Tapse[c] (cm)	FC[d]	6-MWD[d] (m)	BNP/ Nt-ProBNP[d] (ng/L)	TR Vmax[d] (m/s)	Tapse[d] (cm)
25	IPAH	After pregnancy	0	0	MAS+TAD	-	86	50	11	2	-	-	-	-	-	2	480	2010	4.6	2
26	Group 5 (sickle cell anemia)	After pregnancy	0	0	BOS	-	55	37	5	3.8	-	-	-	-	-	3	345	567	4.4	2.5
27	IPAH	Before pregnancy	DILTIAZEM	DILTIAZEM	BOS+SIL+SEL[b]	IV Iloprost	67	42	9	2.8	3	350	36	2.6	2.5	3	240	4241	3.4	1.1
28	IPAH	After pregnancy	0	0	MAS+TAD	-	72	50	10.94	2.19	-	-	-	-	-	4	10	-	3.74	-
29	Eisenmenger	Before pregnancy	MAS+TAD	SIL	MAS+SIL	IV Iloprost	97	63	8.2		3	370	170	5	2	-	-	-	-	-
30	Segmental PAH (complex congenital)	Before pregnancy	BOS+TAD	SIL	BOS+TAD	Milrinon, NE, Epinephrine	125	77	-	-	2	470	116	4.9	2.5	-	-	-	-	-
31	Large systemic-to-pulmonary shunt-APAH	Before pregnancy	MAS	SIL	0	IV Iloprost, dopamine, NE, epinephrine	95	61	5.8	1.6	3	365	118	5.5	-	-	-	-	-	-
32	APAH-CTD	After pregnancy	0	0	BOS+TAD	-	76	54	14	2.2	-	-	-	-	-	4	10	1140	5.8	2
33	Eisenmenger	Before pregnancy	MAS+TAD	SIL	MAS+TAD+SEL	IV Iloprost, dobutamine, NE	94	72	12.7	2	3	390	293	4.7	2.7	3	405	548	4.5	2.6
34	Eisenmenger	After pregnancy	0	0	MAS+TAD+TREP	-	155	106		3.8	-	-	-	-	-	3	334	-	5	1.4
35	IPAH	After pregnancy	0	0	BOS	-	113	66	20	2	-	-	-	-	-	3	275	2706	4.5	1.2

[a]Because the patient lived in the rural area, she did not come to follow-up visits. She used bosentan during pregnancy. The terratogenic effect of bosentan was not observed in the fetus; [b]control cardiac catheterization was performed after delivery. Vasoreactivity test was negative and bosentan was added to the therapy. Sequential triple combination therapy was continued within 1 year; [c]parameters while pregnant at third trimester except patient who was performed threapautic abortus; [d]parameters after pregnancy within 6 months.
APAH, associated pulmonary artery hypertension; BNP, brain natriuretic peptide; BOS, bosentan; CI, cardiac index; CTD, connective tissue disease; IPAH, idiopatic pulmonary arteriel hypertension; Mas, masitentan; NE, norepinephrine; PASP, pulmonary artery systolic pressure; PAMP, pulmonary artery mean pressure; PVR, pulmonary vascular resistance; Sel, selexipag; Sil, sildenafil; 6MWD, 6-minute walking distance; TAD, tadalafil; TR Vmax, tricuspid regurgitation maximal velocity.

Table 5. Comparison of the Clinical, Laboratory, Echocardiographic, and Invasive Hemodynamic Characteristics Between Survivors and Non-survivors in the Pregnant Group with PH

	Survivor (n = 22)	Non-survivor (n = 13)	*P*
Clinical variables			
Age (years)	29.7 (26.3-36.5)	26.7 (25.3-28)	.07
Follow-up duration (day)	535 (367-980)	480 (197-1321)	.74
NYHA 1 (n, %)	-	-	.01
NYHA 2 (n, %)	3 (13.6)	4 (30.8)	
NYHA 3 (n, %)	15 (68.2)	2 (15.4)	
NYHA 4 (n, %)	4 (18.2)	7 (53.8)	
6-MWD	345 (275-380)	323 (185-378)	.72
Blood oxygen saturation (%)	96 (93-97)	84 (81-95.5)	.13
Heart rate (beats/min)	94 (71.5-111)	109 (88-111)	.12
Systolic blood pressure (mm Hg)	100 (91.5-106)	110 (110-120)	.22
Labarotory parameters			
Nt-ProBNP (pg/mL)	411 (241-1300)	340 (115-2395)	.56
Hemoglobin (g/dL)	13 (10.6-14.5)	14 (12.6-14.9)	.39
Echocardiographic parameters			
Tricuspid regurgitation peak velocity (m/s)	4.4 (3.9-5.0)	5.0 (4.8-5.5)	.09
Pulmonary artery systolic pressure (mm Hg)	91 (68-110)	97 (90-105)	.41
Pulmonary artery mean pressure (mm Hg)	56 (49-65)	71 (59-73)	.68
Right atrial pressure (mm Hg)	8 (6-10)	10 (5-12.5)	.78
Right atrium area (cm^2)	17.1 (14.4-23.5)	17.3 (14.9-19.6)	.59
Pulmonary artery diameter (centimeter)	3.6 (3-3.90)	3.0 (2.7-3.9)	.29
TAPSE (centimeter)	1.7 (1.5-2.0)	1.8 (1.6-2.2)	.48
TDI St (cm/s)	12 (11.1-13)	10 (9.9-13.6)	.35
Ejection fraction (%)	65 ± 0.3	64.2 ± 1.9	.07
Right heart catheterization			
Aortic systolic pressure (mm Hg)	123 (105-136)	115 (98-1329)	.26
Aortic diastolic pressuse (mm Hg)	71 (65-81.5)	70 (64.5-76.5)	.62
Aortic mean pressure (mm Hg)	91 (84-102)	84,5 (74-90)	.06
LVEDP-PCWP (mm Hg)	8 (6-10)	11 (9.5-12.3)	.07
Pulmonary artery systolic pressure (mm Hg)	98.5 (77-115)	96 (75-125)	.99
Pulmonary artery mean pressure (mm Hg)	44.5 (32.5-53)	37 (25-58)	.99
Cardiac output (L/min)	4 (3.1-4.8)	3.3 (2.75-3.9)	.19
Cardiac index (L/min/m^2)	2.3 (2-2.9)	1.9 (1.6-2.45)	.16
Transpulmonary gradient (mm Hg)	53 (39-63)	55 (41.5-65)	.98
Trans systemic gradient (mm Hg)	86 (81-97)	77 (70-83)	.01
Pulmonary vascular resistance (Woods Unit)	11.8 (9.1-16.5)	8.9 (8.0-11.0)	.24
Systemic vascular resistance (Woods Unit)	21.6 (17.5-25.3)	20.7(18.3-22.8)	.65
PVR/SVR ratio	0.53 (0.36-0.72)	0.50 (0.42-0.54)	.70
Etiological variables			
IPAH (n, %)	12 (55)	6 (46)	.733
APAH-CTD (n, %)	1 (4)	-	.999
APAH-CHD (n, %)	8 (36)	4 (31)	.999
Eisenmenger	6 (27)	2 (15)	.680
Large systemic-to-pulmonary shunt	0 (0)	1 (8)	.371
Post defect-closure	2 (9)	1 (8)	.999
Group 5 (n, %) (sickle cell anemia)	-	1 (8)	.999
Segmental PAH (complex congenital) (n,%)	1 (5)	2 (15)	.541

TAPSE, tricuspid annular plane systolic excursion; TDI St, tissue Doppler imaging peak systolic tricuspid annular velocity; PVR/SVR, pulmonary vascular resistance/systemic vascular resistance ratio; IPAH, idiopathic pulmonary arterial hypertension; APAH-CTD, connective tissue disease-associated pulmonary arterial hypertension; LVEDP, left ventricular end-diastolic pressure; NYHA, New York Heart Association.

higher in idiopathic PAH as compared to those in other PH subsets, and all deaths occurred in the post-delivery period. Mortality rates were 3.3% in the first week and 2.6% in the period between the first week and the sixth month. Late maternal mortality also correlated with the PH severity.[14]

National trends and in-hospital outcomes in pregnant women with heart disease in the United States have been reported in serial analyses.[7,22-24] Healthcare Cost and Utilization Project's National Inpatient Sample based on hospital admissions for delivery in pregnancies with heart diseases from 2003 to 2012 revealed that women with PH accounted for 6% of these and was associated with a 1% in-hospital mortality rate.[22] Pregnancies with heart diseases have been found to be significantly increased by 24.7% which is related to increases in the frequencies of cardiomyopathies, ACHD, and PH over this time period.[22] In a study based on data from 4 tertiary North American sites, maternal mortality rate in overall pregnancies with severe PH and those with PAH were 16% and 23%, respectively.[23] Deaths that occurred postpartum early period, they were found to be higher with vaginal delivery versus cesarean (33% vs. 22%). Severity of PH was associated with increased risks for preterm delivery, need for utilizations of inotropes, pulmonary vasodilators, and ECMO support but not with risk of neonatal death.[23] In other reports, presence of PH versus absence of any heart disease was found to be associated with a 67 times increased risk for major adverse cardiac events in pregnancies, and this risk increased up to 62% in cases with combinations of these pathologies.[24] The complexity of ACHD was correlated with increased utilization of cesarean delivery and 79 times increased risk of maternal in-hospital mortality.[24]

In a Chinese study based on retrospective analysis of pregnant women with severe PAH who underwent cesarean delivery, perioperative severe PH crisis rate was 19.6% and was related to 63% of mortality.[25] A larger left ventricular end-diastolic diameter, orally taken sildenafil therapy, and a higher pulse oxymetric saturation % at room air prevent but the need for Swan-Ganz catheter placement increases the risk of PH crisis.[25] Despite the improvements in the current PAH treatment strategies over decades, recent reports from the Chinese population continue to document increased maternal mortality in pregnant women,[17,26] and this risk has been correlated with the severity of the background PH and complexity of structural heart diseases.[28]

Currently available 3 ESC guidelines and AHA/ACC 2018 ACHD guidelines have recommended to avoid pregnancy in patients with PAH.[1,5,7,9,20] Moreover, it should be kept in mind that bosentan may reduce the efficacy of oral contraceptive agents.[1,5,7,9] The patient who becomes pregnant should be informed about the high risk, and termination of the pregnancy should be discussed with family. These guidelines have pointed out the increased fetal and neonatal mortality, in the presence of preterm delivery, reduced maternal cardiac output and/or hypoxemia as defined by the presence of oxygen saturation below 85% at rest.[1,5,7,9,20] Severity of PAH, late hospitalization, and the use of general anesthesia have been considered as risk factors for maternal death, and these women should be managed by a multidisciplinary team, with a PH expert included in an expert center for pregnancy and cardiac disease.[1,5,7,9,20] Patients who choose to continue pregnancy should be managed with PAH therapies except for Endothelin receptor antagonist (ERAs) and planned elective delivery. In treatment-naive pregnant women with PAH, initiating the treatment should also be considered.[1,5,7,9,20] Avoiding general anesthesia is essential, and in the absence of specific reasons for cesarian delivery, vaginal delivery is usually the preferred mode.[1,5,7,9,20] However, cesarean delivery should be considered for obstetrical indications or in patients with ES, severe heart failure, or pre-term labor while on oral anticoagulants.[5,7,9,20] But the optimal time of delivery in pregnant women with PAH remaining stable and a well-developed fetus need to be determined. There is no robust evidence favoring earlier termination of pregnancy in terms of maternal outcomes.

In our patients, modification in targeted therapies by switching to sildenafil from other targeted drugs has been documented to provide an event-free maternal course until delivery time. Section procedures were also well tolerated whereas sudden clinical deterioration in the first days of post-delivery period was the main characteristic of these patients and it resulted in mortality in 41.6% of patients despite the pro-active strategies including mechanical ventilation, ECMO, inotropic support, and potent vasodilatory therapies.

Study Limitations

Population size of pregnant patients with PH, single-center enrolment of all patients, retrospective nature of analysis, and the lack of any proven predictor for clinical deterioration after delivery may be considered as limitations of this study. Fortunately, mainly as a result of the consulting risk of gestation, the number of pregnancies was limited in our productive female patients with PH. However, multicenter registries and prospective studies might provide new perspectives for risk prediction and better management strategies in this setting. Immortal time bias cannot be excluded in patients without any PAH diagnosis before gestation.

CONCLUSION

In conclusion, despite the development of advanced therapies in PAH, pregnancy, particularly in women with idiopathic PAH, remains to be associated with high mortality. Therefore, avoiding pregnancy is essential in patients with severe PAH, and decision for the termination of the pregnancy should be discussed in this setting. Patients who prefer to continue pregnancy should be managed with PAH-targeted therapies, except for ERAs, close follow-up by multidisciplinary teamwork, and planned elective delivery without general anesthesia.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of Koşuyolu Heart Education and Research Hospital (approval no: 2013.3/4).

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