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Management of anesthesia in pregnant women with pulmonary hypertension

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Abstract. – OBJECTIVE: Pulmonary hypertension (PH) is a rare heart disease associated with high maternal and fetal mortality. This study aims to discuss anesthesia management and the fetal and maternal outcomes of patients with PH followed-up at our clinic.

PATIENTS AND METHODS: This study includes a retrospective analysis of 105 pregnant women with PH. The patients were classified according to the mean pulmonary artery pressure (mPAP) values measured at rest by transthoracic echocardiography. The first group included patients with an mPAP value between 25 and 49 mmHg, considered to have a mild PH, whereas patients with an mPAB value ≥50 mmHg were considered to have severe PH and were included in the second group.

RESULTS: When the patients were examined for etiology, the majority (n=84, 70.5%) were found to have type 2 PH. It was found that in pregnant women with severe PH, the diameters of the left atrium, right atrium, and right ventricle were significantly larger (p=0.008, p=0.04, and p=0.013, respectively), and the ejection fraction was also significantly lower (p=0.04).

CONCLUSIONS: Although there has been a partial decrease in mortality for PH in recent years, it is still a serious condition that requires a multidisciplinary approach and well-planned obstetric treatment.

Key Words:
Pulmonary hypertension, Mean pulmonary artery pressure, Pregnancy, Anesthesia management.

Introduction

Pulmonary hypertension (PH), defined as mean pulmonary artery pressure (mPAP) ≥25 mmHg at rest, is a rare and severe clinical syndrome characterized by pulmonary remodeling and increased pulmonary vascular resistance[1,2]. Epidemiological data on PH indicates that women are 3-4 times more susceptible to developing PH than men. Current findings suggest that sex hormones play a significant role in pulmonary vascular disease. Moreover, women diagnosed with PH are frequently young and within childbearing age[3,4]. How pregnancy-related changes in sex hormones might affect pregnant patients with PH is currently a matter of intense debate. In addition, it is a concern that the physiological burden of pregnancy in patients with PH is associated with high maternal and fetal mortality[5]. PH-related mortality generally results from the inability of the right ventricle and pulmonary vascular structure to adapt to cardiovascular changes during pregnancy and postpartum[6]. Cardiac output (CO) increases during pregnancy and can reach up to 9 L/min in the terminal period[7,8]. Moreover, the increase in progesterone and nitric oxide causes a decrease in systemic and pulmonary vascular resistance (PVR)[9]. However, because pulmonary vascular elasticity is impaired in women with PH, pregnancy-related PH causes higher CO suppression of the right ventricle, leading to an increase in PVR.

Since pregnancy is associated with high maternal mortality (30-56%) in patients with PH, the World Health Organization (WHO)[10], which defined the mean pulmonary artery pressure at rest as (mPAP) ≥25 mmHg, recommends avoiding pregnancy. However, right heart catheterization (RHC) is an invasive procedure in patients with PH who develop pregnancy, and although it is the gold standard diagnosis for PH, transthoracic echocardiography is currently used for screening[11]. The 2013 WHO updated PH classification divided PH into five groups based on etiology:

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pulmonary arterial hypertension (group 1); PH resulting from a disease in the left ventricle (group 2); lung disease (group 3); thrombotic disease (group 4); and multifactorial etiologies (group 5)[12].

Prognosis in PH pregnant women has improved with the emergence of new targeted therapies and using a multidisciplinary approach[13-15]. Although pregnancy seems safer today, mortality remains high in women with PH[16,17]. The greatest risk period is the puerperium and the early postpartum period. The severity of PH, delay in hospitalization, and perhaps the use of general anesthesia (GA) are risk factors for maternal death[6]. Regional anesthesia (RA) is generally preferred to GA[18]. Optimizing fluid balance and right ventricular (RV) function are vital predictors of favorable outcomes. For treatment, a tailored approach is essential, with many units initiating treatment with oral sildenafil. Bosentan and other endothelin receptor antagonists are linked to embryopathy and should be discontinued unless there is a substantially elevated risk to the mother. Patient subgroups that respond well to calcium channel blocker (CCB) therapy and demonstrate a genuine vasodilator response carry a lower risk. Thromboembolism poses a significant threat, and thus, anticoagulant therapy can be introduced. Additionally, diuretics might be necessary for patients exhibiting heart failure[10].

This study aims to divide pregnant women with PH who underwent a cesarean section at the Dicle University operating room into two groups – mild and severe PH – according to their mean pulmonary artery pressure and to define the clinical features, treatment and multidisciplinary management strategies, and maternal-fetal outcomes of PH in these groups.

Patients and Methods

This study was initiated after obtaining approval from the Ethics Committee of Dicle University Faculty of Medicine Non-Interventional Clinical Research dated June 9, 2022 (number 170). This retrospective cross-sectional study was conducted in accordance with the Helsinki Declaration of Human Rights.

In our study, anesthesia methods applied to pregnant patients with high average pulmonary artery pressure who were operated at the Dicle University Hospital between January 2016 and December 2021 were evaluated. The weeks post-delivery, maternal age, the diagnosis of cardiac disease, cardiac operation history (if any), and mortality and morbidity conditions of the pregnant women were recorded in this study. The American Society of Anesthesiologist (ASA) classification of patients, type of anesthesia, the use of intraoperative inotropes, and length of stay in intensive care units were recorded. The APGAR scores and birth weights of newborns were also recorded. This scoring system provides a standardized assessment for infants after delivery. The APGAR score compromises 5 components: (1) color, (2) heart rate, (3) reflexes, (4) muscle tone, and (5) respiration.

PH was defined as exhibiting an mPAP value of ≥25 mm Hg. A mPAP value between 25 and 49 mmHg, compared to the highest value measured during pregnancy, was considered mild, whereas a condition of ≥50 mmHg was defined as severe PH[12,19-21]. Transthoracic echocardiography records of the patients were analyzed for mean pulmonary artery pressures. In our retrospective study, invasive RHC could not be performed. We had a total of 107 patients with an mPAP value of ≥25 mmHg. Two of these patients were excluded because they had twin pregnancies. The patients with an mPAB value between 25 and 49 mmHg were classified as Group 1, and those with a value ≥50 mmHg were classified as Group 2. Group 1 and Group 2 consisted of 84 and 21 patients, respectively. The patients in the groups were compared for the following parameters: age, gravidity parity, length of stay in the intensive care unit, hemoglobin levels, type of anesthesia, ASA intraoperative inotropic agent use, tubal ligation, drug treatment for PH, etiology, echocardiography (ECHO) findings, and APGAR scores.

Statistical Analysis

SPSS 24.0 software for Windows (IBM Corp., Armonk, NY, USA) was used for the statistical analysis. Continuous data are expressed as mean, and standard deviation and categorical data are expressed as frequency and percentage. The categorical data of the groups were compared using the Chi-square and Fisher's exact tests. The Kolmogorov-Smirnov test was used to determine whether the numerical data were normally distributed. The Student's *t*-test was used to analyze data with a normal distribution, while the Mann-Whitney U test was used to analyze non-normally distributed data. In all comparisons, $p<0.05$ was considered significant.

Results

A total of 107 patients were included in the study. Two patients were excluded from the study because they had twin pregnancies, and the study was completed with 105 patients. The mean age of the patients included in the study was 30.45 years. The demographic and clinical characteristics of the patients are shown in Table I.

When the etiology of the patients was examined, it was found that the majority of our patients had type 2 PH (rheumatic valve disease, heart failure, subaortic membrane, etc.). Of these patients, 68 were in the mild PH, while 16 were in the severe PH group. Ten of 15 patients who had type 1 PH group [Atrial Septal Defect (ASD), Ventricular Septal Defect (VSD), Patent Foramen Ovale (PFO), combined congenital heart diseases, Marfan syndrome], were in the mild PH group, and 5 patients were in the severe PH group. All type 3 PH patients (6) were also in the mild PH group. Nine of our patients underwent cardiac surgery, and two of them underwent mitral valve replacement, one underwent subaortic membrane repair, two underwent ASD closure, two underwent outlet VSD closure, one underwent aortic aneurysm, and one underwent VSD-PDA closure surgery.

When the groups were compared in terms of demographic and clinical characteristics, it was

Table I. Demographic data of patients.

Characteristic	Group 1 (Mild PAH, n = 84)		Group 2 (Severe PAH, n = 21)		*p*-value
	Mean	SD	Mean	SD	
Age (yr)	30.95	6.21	28.47	6.19	0.74
Gravidity	3.96	2.11	2.66	1.87	**0.008**
Parity	2.54	1.92	1.38	1.53	**0.009**
Hemoglobin (g/L)	11.13	1.78	11.23	1.57	0.817
Intensive care hospitalization period	3.08	1.46	3.09	1.81	0.784
	Frequency	Percent	Frequency	Percent	
Type of Anesthesia					
General	36	42.9	12	57.1	0.24
Regional	48	57.1	9	42.9	
ASA					
2	54	64.3	9	42.9	**0.046**
3	29	34.5	10	47.6	
4	1	1.2	2	9.5	
Use of inotropic agent					
Used	16	19	6	28.6	0.337
Not used	68	81	15	71.4	
Tubal ligation					
Done	40	47.6	7	33.3	0.239
Not done	44	52.4	14	66.7	
Drug use					
ERA-PDEI	0	0	4	19	**< 0.001**
Diuretic	6	7.1	1	4.8	
CCB	2	2.4	0	0	
Anticoagulant	18	21.4	1	4.8	
Combined	15	17.9	13	61.9	
No Drug	43	51.2	2	9.5	
Etiology (WHO PH group)					
Type 1	10	11.9	5	23.8	0.200
Type 2	68	81	16	76.2	
Type 3	6	7.1	0	0	

ASA: American Society of Anesthesiologist; ERA: Endothelin Receptor Antagonist; PDEI: Phosphodiesterase Inhibitor; CCB: Calcium Canal Blocker; WHO: World Health Organization; PH: Pulmonary hypertension; PAH: Pulmonary Arterial Hypertension.CCB: Calcium Canal Blocker; WHO: World Health Organization; PH: Pulmonary hypertension; PAH: Pulmonary Arterial Hypertension.

Table II. Relationship between pulmonary arterial pressure and APGAR score.

	Group 1 (Mild PAH, n = 84)		Group 2 (Severe PAH, n = 21)		*p*-value
	Mean	SD	Mean	SD	
Neonatal 1-min APGAR	5.42	1.67	5.52	2.33	0.993
Neonatal 5-min APGAR	7.72	1.75	7.76	2.16	0.761
Birth weight (gr)	2630.03	746.28	2616	841	0.27
Delivery week	35.71	3.86	35.09	3.65	0.917

PAH: Pulmonary Arterial Hypertension. APGAR: This score comprises 5 components: (1) color; (2) heart rate; (3) reflexes; (4) muscle tone; and (5) respiration.

found that the gravidity and parity ratios of the patients in Group 1 were statistically significantly higher (p=0.008; p=0.009). In addition, the ASA score was found to be statistically significantly higher in patients in Group 2 (p=0.046). At the same time, it was found that patients in Group 2 had a statistically significant higher drug use (p<0.001). It was determined that there was no statistically significant difference between the groups in terms of age, hemoglobin, tubal ligation rate, length of stay in the intensive care unit, anesthesia method applied, and inotropic agent requirement (p>0.05) (Table I).

When the patients in the groups were compared according to the characteristics of the newborns, no statistically significant difference was found between the two groups in terms of APGAR scores at 1 and 5 minutes after birth, birth weight, and delivery week of the infants (p>0.05) (Table II). When the groups were compared in terms of ECHO findings, it was found that the LA, RA, and RV diameters of the patients in Group 2 were statistically significantly higher than those in Group 1, and the ejection fraction (EF) values were found to be lower than those in Group 1 (p=0.008, p=0.04, p=0.013, p=0.04). No significant difference was found in both groups in terms of LV diameter values (p>0.05) (Table III).

When the patients were grouped as general and RA according to the type of anesthesia applied, the 1-min APGAR scores of the infants of the patients who received GA were statistically significantly lower than the RA group (p=0.005). It was determined that there was no difference between the patients who underwent general and regional anesthesia in terms of 5-min APGAR scores and intensive care hospitalization duration (p>0.05) (Table IV).

Discussion

At the end of this study, in which the clinical features of pregnant women with PH who underwent cesarean section, multidisciplinary management strategies with treatment, and maternal-fetal outcomes of PH were defined, it was found that the diameters of the left atrium, right atrium, and right ventricle were larger in pregnant women with severe PH, while ejection fraction was found to be lower.

Table III. Echocardiographic data in patients with PAH.

	Group 1 (Mild PAH, n = 84)		Group 2 (Severe PAH, n = 21)		*p*-value
	Mean	SD	Mean	SD	
% EF	59.64	6.43	57.38	7.84	**0.04**
LA diameter (mm)	4.09	0.707	4.55	0.65	**0.008**
LV diameter (mm)	4.59	0.63	4.61	0.78	0.997
RA diameter (mm)	3.43	0.61	3.88	0.9	**0.04**
RV diameter (mm)	3.33	0.52	4.61	0.78	**0.013**

% EF: Ejection Fraction; LA: Left Atrium, LV: Left Ventricular, PAH: Pulmonary Arterial Hypertension, RA: Right Atrium, RV: Right Ventricular.

Table IV. The Relationship Between Anesthesia Method and APGAR score and intensive care hospitalization.

	General Anesthesia		Regional Anesthesia		
	Mean	SD	Mean	SD	*p*-value
Neonatal 1-min APGAR	5.04	1.78	5.78	1.78	0.005
Neonatal 5-min APGAR	7.52	1.77	7.91	1.77	0.135
Intensive care hospitalization Duration	3.39	1.78	2.82	1.24	0.13

APGAR: This score comprises 5 components: (1) color, (2) heart rate, (3) reflexes, (4) muscle tone, and (5) respiration.

In the literature, various studies have examined pregnant patients with pulmonary hypertension. For instance, in their retrospective study of 79 pregnant patients with PH, Luo et al[22] found no significant difference in ejection fraction and cardiac output (CO) between those with mild and severe PH. However, consistent with our findings, they[22] observed that the right atrial diameter and right ventricular diameter were statistically larger in patients with severe PH.

When pulmonary hypertension is evaluated in terms of etiology, it is seen that the most common cause is PH due to left heart diseases[23]. In our study, there were mostly type 2 PH patients, and the most common cause was rheumatic valve disease.

There is no definitive guidance regarding the optimal anesthesia method for patients with PH[18]. Nevertheless, past research[6,18] has highlighted that PH patients undergoing general anesthesia (GA) face a risk of death four times higher than those receiving regional anesthesia. In addition, in a prospective observational study[14], it was stated that all pregnant PH patients who died after delivery had been administered GA. It remains unclear whether these observations reflect the harmful effects of GA, rather than being the result of a bias of choice associated with administering GA to pregnant women with a worse general condition[18]. However, there is also a consensus recommending the application of RA in pregnant women with PH[24].

In our study, when the APGAR scores of the infants of the patients to whom we applied GA and RA were compared, we found that the 1-minute APGAR scores of the infants of the patients in the GA group were statistically significantly lower, but the 5-minute APGAR scores were similar. We associated this situation with the worsening general condition of the pregnant women to whom we applied GA. Khan et al[25] compared the APGAR scores of the infants of the pregnant women they followed under GA and RA and found that the APGAR scores were higher in the RA group than in the GA group. These results are consistent with the results of our study.

In a study, Safdar et al[7] examined 17 pregnant idiopathic pulmonary arterial hypertension (IPAH) patients; they reported that maternal death occurred in 3 (17.6%) patients up to 1 week after delivery. Sanges et al[26] examined 149 pregnant women with PH between 2005 and 2012 and stated that the overall maternal mortality rate was 6% in this series. In a prospective study[17] conducted with 151 pregnant women with PH, Sliwa et al[17] found the maternal mortality rate below 5%. On the same subject, Monagle et al[20] reported the mortality rate as 5% in the pregnant women with PH they followed, while Keepanasseril et al[27] reported the mortality rate as 4.9%. However, in the study of Keepanasseril et al[27] the mortality rate was found to be higher in patients with Eisenmenger syndrome and idiopathic PAH. In our study, one of 21 pregnant women with severe PH died, and this rate was 4.76%. The patient who died had developed Eisenmenger syndrome.

Luo et al[22] found no significant difference between the groups in terms of infant birth weights in pregnant women with PH, whereas they found the delivery weeks and APGAR scores of infants significantly lower in the severe PH group. In our study, we did not find a statistically significant difference between the groups in terms of the delivery week, infant birth APGAR score, and birth weight of infants.

With the introduction of advanced therapeutic alternatives to the treatment of pregnant women with PH, regression in symptoms, increased functional capacity, and satisfactory survival rates have been observed[16]. Ekinci et al[28] reported that 50% of the patients in the severe PH group and only 25% of the patients in the moderate PH

group received advanced treatments. The rate of anticoagulant use was 81%. Meng et al[21] divided patients into two groups – mild and severe PH – and stated that 73% of patients with severe PH and 32% of patients with mild PH received further treatment. In the same study, the rate of anticoagulant use was found to be 83%. In the study by Keepanasseril et al[27] advanced PAH drug use was observed in 31.3% of pregnant women. Luo et al[22] reported that 32.3% of patients received PH-specific treatment (diuretic, sildenafil, and treprostinil) a few weeks before delivery. In our study, four pregnant women with severe PH used endothelin receptor antagonist and phosphodiesterase inhibitor before pregnancy. In addition, 17.9% of pregnant women with mild PH and 61.9% of pregnant women with severe PH had been administered combined (diuretic, anticoagulant) treatment. While 51.2% of the mild PH pregnant women did not use any medication, 9.5% of the severe PH pregnant women (2 of them uncontrolled pregnancies) did not have a history of drug use.

Since right ventricular catheterization during pregnancy was considered an invasive procedure in our study, the diagnosis of PH was made only by transthoracic and transesophageal echography. Therefore, we could only show the changes in echocardiography. This situation stands as a limitation of our study. A second limitation is that our study is a retrospective and single-center study. Prospective and multicenter studies on the subject are needed.

Conclusions

Pregnancy in patients with PH still maintains its seriousness despite the decreasing maternal mortality rate. In every patient with PH who has the potential to give birth to a child, pre-pregnancy counseling should be performed. In particular, patients with worsening right heart failure during early pregnancy should be offered the option of terminating their pregnancy. However, if they plan to continue the pregnancy, PH treatment should be arranged to increase the chances of a positive outcome. In this context, a multidisciplinary approach with an obstetrician, a cardiologist dealing with PH, and an anesthesiologist is highly recommended. However, despite the multidisciplinary approach, mortality rates in pregnant patients with PH continue to be high.

Conflict of Interest
The authors declare that they have no conflict of interests.

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Ethics Approval
This study was initiated after obtaining approval from the Ethics Committee of Dicle University Faculty of Medicine Non-Interventional Clinical Research dated June 9, 2022 (number 170).

Availability of Data and Materials
All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

Informed Consent
Written informed consent was obtained from all patients and/or their guardians.

Authors' Contribution
All authors contributed to the study's conception and design. The first draft of the manuscript was written by HTS, OU, and SS, and all authors commented on previous versions of the manuscript. Material preparation: HTS and ZBY. Data collection: ZBY and EB. Analysis was performed by HTS and OU. Review and editing: SS, ZBY, and MK. All authors read and approved the final manuscript.

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