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ORIGINAL ARTICLE

MANAGEMENT AND OUTCOME OF SEVERE PULMONARY HYPERTENSION IN PREGNANCY: EXPERIENCE FROM A UNIVERSITY HOSPITAL IN NORTHERN ETHIOPIA

Abraha Hailu MD[1*], Awol Yeman ,MD[2], Ermias Abate MD[2], Hale Teka MD[2], Haftom Berhane BSc[3], Anna Whelan MD[4], Joan Briller MD[5], Heather Nixon MD[6], Hagos Godefay, PhD[7], Gelila Goba MD MPH[4]

ABSTRACT

Introduction: *Pulmonary hypertension is a rare disease and, when associated with pregnancy, it can be devastating. In the developed world, maternal mortality from pulmonary hypertension has decreased from 56% in the 1970s to 16% in 2014. In developing nations, there are still challenges in managing these cases.*
Objective: *We reviewed management outcome in patients with severe pulmonary hypertension managed in a resource limited setting during the period September 1, 2016 - September 30, 2017.*
Methods: *Cases with severe pulmonary hypertension were prospectively recruited from high-risk antenatal care follow up and cardiology clinics and wards. We studied severity and type of pulmonary hypertension, New York Heart Association functional status, mode of delivery and anesthesia as well as neonatal and maternal outcomes.*
Results: *Twenty-one cases with severe pulmonary hypertension were included. Seventeen of the patients had rheumatic heart disease (Group 2 pulmonary hypertension, with average mitral valve area of 0.9sqcm), one had membranous ventricular septal defect (Group 1 pulmonary hypertension) and three had both congenital heart disease and rheumatic heart disease. The mean (SD) pulmonary arterial pressure as measured by echocardiography was 102.9 (±16.9) mmHg. Fourteen (66.7%) patients had New York Heart Association class III or more, 10 had cesarean section deliveries, and five had vaginal deliveries. There were four (19.1%) maternal deaths with a mean (SD) age at death of 28 (±5.3) years.*
Conclusion: *Pulmonary hypertension is mostly associated with rheumatic heart disease, which still prevails among pregnant mothers in our setting. Further studies are recommended on multi-disciplinary* team management *approaches in patients with severe pulmonary hypertension in pregnancy.*
Key words: *pulmonary hypertension, pregnancy, Ethiopia*

INTRODUCTION

Pulmonary hypertension (PH) is a hemodynamic and pathophysiological condition characterized by abnormally elevated pressures in the pulmonary vasculature. It is defined as a mean pulmonary arterial pressure ≥ 25 mmHg at rest measured using right heart catheterization (1,2). PH can be caused by an increase in pulmonary blood flow, pulmonary vascular resistance, pulmonary venous pressure or a combination of these factors.

Pregnancy outcomes in patients with PH remain poor despite advanced therapies. Although experts and consensus guidelines recommend against pregnancy in PH, it may nonetheless occur not infrequently especially in developing nations, where the access to health care, particularly prenatal counseling, is limited and some mothers get pregnant regardless of medical recommendations.

Although recent studies suggest improved outcomes in the modern era, maternal morbidity and mortality clearly remain high. PH is a rare disease and when associated with pregnancy can be devastating. In the developed world, maternal mortality from PH has decreased from 56% in the 1970s to 16% in 2014. In the developing world, there are still many challenges in the management of these cases (1,2).

The highest risk is in the peripartum and immediate postpartum period. The increased mortality risk is due to poor tolerance of pregnancy related hemodynamic and physiologic changes that can precipitate right ventricular (RV) failure and arrhythmias. These changes begin in the first trimester and continue for weeks into the postpartum period. In the era of modern pulmonary arterial hypertension (PAH) therapies and care, maternal mortality rates in PAH appear to have declined, recently reported at 17%–33%, even though this is still high (3,4).

[1]Mekelle university – College of Health Sciences; cardiology unit, department of internal medicine, Ethiopia.
[2]Mekelle university – College of Health Sciences, department of Obstetrics and Gynecology, Ethiopia.
[3]Mekelle university – College of Health Sciences, department of Anesthesia, Ethiopia. [4]University of Illinois, Department of Obstetrics and Gynecology, Chicago, USA. [5]University of Illinois, Cardiology, Chicago, USA. [6]University of Illinois, Department of anesthesiology, Chicago, USA.
*Corresponding Author E-mail: abrahahailu45@yahoo.com

Management of these high-risk pregnancies involves a systematic multidisciplinary team approach with pulmonary hypertension experts, cardiologists with expertise in managing cardiac disease in pregnancy, obstetricians and cardiac anesthetists with the goal of minimizing maternal and fetal death.
Mortality in pregnant women with PH is high, reportedly as high as 30% for primary PH, 36% for Eisenmenger's syndrome, and 50% for secondary PH (3,). However, a systematic review of the outcome of PH in pregnancy showed a significant decline in maternal mortality from 38% during 1978–1996 to 25% during 1997–2007, suggesting advanced therapies and a multidisciplinary approach might have results in better outcomes (3).

Data on the underlying causes of pulmonary hypertension in general and during pregnancy in particular in the developing world, especially in sub-Saharan Africa, are limited. Experience on maternal and neonatal outcomes and prepartum, intrapartum and postpartum care of high-risk mothers is limited. We describe in this study the pregnancy outcome and management approaches in a series of 21 pregnant mothers with PH a university hospital in Northern Ethiopia.

PATIENTS AND METHODS

A prospective registry was undertaken of all patients admitted to Mekelle University College of Health Sciences Ayder Comprehensive Specialized Hospital for management of PH in pregnancy between September 1, 2016 and September 30, 2017. The hospital is located in Mekelle City, Tigray region, Northern Ethiopia and has a bed capacity of 500 - 108 for gynecology and obstetrics, 108 for internal medicine, and eight for adult intensive care unit (ICU). The labor and delivery suite of the hospital has 50 beds and serves some 5000 delivers annually.

Cases with severe PH were identified from high-risk antenatal care follow up, cardiology and general internal medicine outpatient clinics and inpatient maternity and medical wards. A data collection tool developed for this purpose was used to collect information prospectively. We reviewed the patients on average every two weeks until delivery and on average every three-four weeks until four months postpartum.

The following clinical data were recorded at initial presentation, and during follow-up and delivery: age, parity, abortion history, gestational age, symptoms, severity and type of pulmonary hypertension, New York Heart Association (NYHA) functional status (at presentation and delivery), timing of delivery (weeks), mode of delivery and peripartum monitoring used for anesthetic management as well as neonatal and maternal outcomes, APGAR scores at 1 and 5 min and birth weight.

The arrival time at the hospital was documented. A cardiologist and an obstetrician in the outpatient and inpatient wards jointly with an anesthetist evaluated patients before, during and after delivery.

Transthoracic echocardiography was used to assess severity of PH and Peak Systolic Pulmonary Artery Pressure (PPAP). Levels above 70 mmHg were considered \Severe PH. We included those with only severe PH in the study. The estimation of systolic PAP was made based on the peak tricuspid re-gurgitation velocity (TRV) taking into account right atrial pressure (RAP) as described by the simplified Bernoulli equation. Other echocardiographic parameters were also recorded to look for the underlying cardiac lesion: valvular thickness, mobility, calcification, Color flow Doppler and Continuous wave Doppler parameters to diagnose for rheumatic changes based on the 2012 World Heart Federation criteria to diagnose rheumatic heart disease (RHD) and assess the severity of valve lesions (25). Cardiac chamber dimension, Left Ventricular Ejection Fraction (LVEF) and evaluation for shunt lesions were made. Echocardiography was repeated if three months elapsed from previous scan and if patient condition worsened.

We developed a standard and emergency medical management plan for each patient, including details of the proposed delivery methods, timing and medical therapy required in the peripartum period. A standard of care was set by the team to counsel the patients on termination of pregnancy if patients were diagnosed with severe PH and presented earlier than 24 weeks of gestation. Patients were followed up if they presented after 24 weeks or refuse termination. Pregnancy was terminated at 37-40 weeks electively via cesarean section unless patient presented in advanced labor or refuses termination. Postpartum patients were kept for 48 in ICU and two weeks in medical ward.

The team also decided on the need for medications such as oral diuretics, beta blockers , digoxin, intramuscular benzathine penicillin, and anticoagulation based on the clinical condition of individual patient / NYHA functional state among others / and the type as well as severity of cardiac lesion. The team anticipated hypotension, pulmonary edema, pulmonary thrombo-embolism, and atrial fibrillation and prepared important intravenous drugs like digoxin, adrenaline/noradrenaline when available, furosemide, metoprolol, and fentanyl were prepared should these complications arise specially during the peripartum period.

Simple descriptive data analysis was done using SPSS version 20 (IBM, Armonk, NY, USA). Institutional ethical approval was obtained for the study from the Health Research Ethics Review Committee of Mekelle University College of Health Sciences.

RESULTS

Twenty-one cases of severe PH were identified. The mean (SD) age was 26.7 (±5.7) years. Sixteen patients had chronic RHD, with average mitral valve area of 0.9sqcm, one had congenital heart defect (CHD) and three had both CHD and RHD (Figure 1). The mean (SD) pulmonary arterial pressure as measured by echocardiography was 1029.(± 16.9) mmHg.

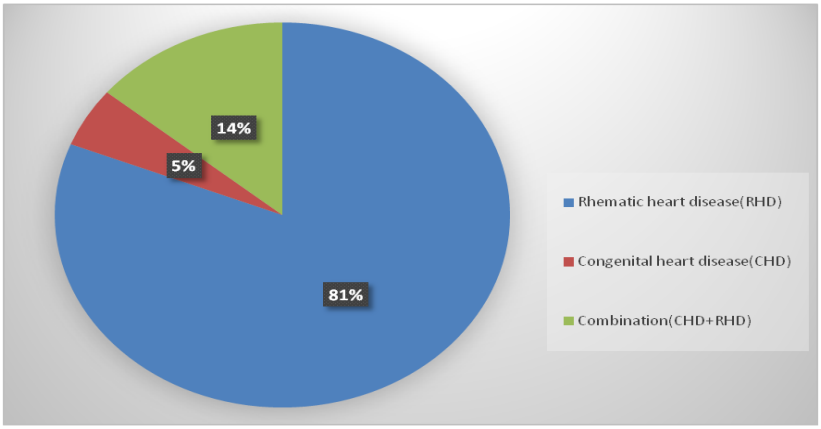

Figure 1: Causes of pulmonary severe hypertension in pregnancy in Ayder Comprehensive Specialized Hospital, September 1, 2016 - September 30, 2017.

The earliest and maximum gestational ages at diagnosis of PH was 12 and 39 weeks, respectively. The minimum and maximum duration of follow up of patients with PH was four and 10 months, respectively. At presentation, 14/21 (66.7%) of the patients had NYHA III and IV, while seven had NYHA functional class II. At the time of delivery, there was an overall improvement in functional status: two were NYHA I, seven were NYHA II, three were NYHA III, and eight were NYHA IV. The major morbidity was heart failure, which occurred in all 21 patients. Preeclampsia with severity features was major obstetric co-morbidity, which occurred in five patients. Over three quarter (76.2%) of pregnancies resulted in live birth (Table 1).

The major morbidity was heart failure, which occurred in all 21 patients. Preeclampsia with severity features was a major obstetric co-morbidity, which occurred in five patients. Over three quarters (76.2%) of pregnancies resulted in live birth. Ten patients underwent cesarean deliveries, three had spontaneous vaginal deliveries, four delivered with instrument assisted second stage.

Two patients had a therapeutic abortion, one with misoprostol at 19 weeks and the other with dilatation and evacuation at 16 weeks of gestation.

There were four (19.1%) maternal deaths, including one late maternal death (fourth month post-partum). Two of these patients were counseled on termination of pregnancy during early second trimester, one died at 26 weeks of gestation before delivery at the hospital intensive and the second died following spontaneous abortion at 26 weeks of gestation after she came to the hospital in NYHA class IV heart failure.

The third patient had antenatal follow up in our hospital and died immediately following the delivery of the placenta. One patient who presented in NYHA class IV heart failure and went home against medical advice to deliver at her nearby health center. She died on her fourth month postpartum. Death was associated with disease progression in two cases and pulmonary venous thromboembolism in one case (Table 2).

Table 1: Demoographic and clinical features of patients with pulmonary hypertension in patiens at Ayder Comprehensive Specialized Hospital, September 1, 2016 - September 30, 2017.

Case #	Age	G, P	Cause of PH	NYHA at Presentation	PPAP	Delivered / terminated at week	Mode of delivery/ termination	6-month post-partum	
								Mother	Neonate
1	25	2, 1	RHD	IV	107	UK	SVD	Died at 4th month post	Alive
2	33	2, 1	RHD	II	117	37.00	LUSCS	Alive	Alive
3	30	4, 3	RHD	II	100	38.00	LUSCS	Alive	Alive
4	21	1, 0	RHD	IV	83	37.00	LUSCS	Alive	Alive
5	19	3, 0	RHD, CHD	IV	136	32.00	LUSCS	Alive	Alive
6	40	8, 7	RHD	IV	83	UK	SVD	Alive	Alive
7	20	1, 0	RHD	IV	134	38.00	LUSCS	Alive	Alive
8	23	2, 1	RHD	IV	97	26.00	NA	Died in ICU	NA
9	25	3, 2	RHD	IV	110	38.00	LUSCS	Alive	Alive
10	22	1, 0	RHD, CHD / PDA/	IV	110	UK	Forceps	Alive	ENND
11	29	1, 0	CHD	II	97	39.00	vacuum	Died immediately	Alive
12	25	1, 0	RHD	II	105	38.00	LUSCS	Alive	Alive
13	22	4, 3	RHD	IV	78	40.00	Forceps	Alive	Alive
14	30	7, 6	RHD	IV	90	UK	LUSCS	Alive	Alive
15	25	2, 0	RHD	II	97	40.00	LUSCS	Alive	Alive
16	23	4, 3	RHD	II	95	38.00	Forceps	Alive	Alive
17	29	2, 1	RHD	III	100	UK	Forceps	Alive	Stillbirth
18	35	7, 6	RHD	IV	110	26.00	SVD	Died post abortion	NA
19	35	9, 8	RHD	III	116	19	Abortion	Alive	NA
20	21	1, 0	RHD, CHD	III	72	38	LUSCS	Alive	Alive
21	28	3,2	RHD	II	123	16	D & E	Alive	NA

G: gravidity, CHD: congenital heart disease, RHD: Rheumatic Heart Disease, PDA: Patent Ductus arteriosus; END: early neonatal death, LUSCS: lower uterine segment cesarean section, NA: not applicable, ICU: Intensive care unit, NYHA: New York- Heart Association, P: parity, PPAP: peak pulmonary arterial pressure, SVD: spontaneous vaginal delivery.

Table 2: Characteristics of the maternal Death

Case #	Age	Type and Severity of the cardiac lesion	PAP	Gestational age at Presentation (weeks)	NYHA at presentation	Mode of delivery	Mode of Anesthesia	Cause of maternal death	Timing of maternal death
1	25	Very Severe MS, Severe MR, Moderate AR, Severe PH	107	36	4	SVD	None	Disease Progression	4th month post-partum*
2	23	Very Severe MS, Severe MR, Severe AS, severe PH, Mild AR,	97	26	4	NA	NA	Disease progression	In ICU ante-partum
3	29	Membranous VSD with Severe PH	97	39	2	Vacuum	Pethidine	Unexplained/ Disease Progression/	Immediate post-partum
4	35	MS, MR	110	25	4	NA	None	Massive PTE	post abortion

MR: Mitral Regurgitation, MS: Mitral Stenosis, AS: Aortic Stenosis, AR: Aortic Regurgitation, PH: Pulmonary Hypertension, VSD: Ventricular Septal Defect, PTE: Pulmonary Thromboembolism; *Late Maternal Death

There was one stillbirth. The mean 1st and 5th minute APGAR score was 6.69 ($\pm$2.27) and 7.88 ($\pm$2.45), respectively. Four neonates were admitted to neonatal ICU of which one neonate died on 6th day of life, the cause of which we have not documented.

DISCUSSION

The World Health Organization (WHO) has reclassified PH in 2008. It differentiates five major groups of pulmonary hypertensive disorders that differ in their pathogenesis, severity, structural abnormalities, prognosis, and management strategies (5); broadly, pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis (Group 1), PH due to left heart disease (Group 2), PH due to lung diseases and/or hypoxia (Group 3), Chronic thromboembolic PH (Group 4), and PH with unclear and/or multifactorial mechanisms (Group 5). In our series, sixteen patients fell under the category of group 2, one patient under group 1, three patients fulfill the criteria for both group 1 and 2.

The underlying etiology of PH could vary from region to region; the leading causes of PH globally are group 2 PH mostly related to Left sided heart failure (23). Our series also confirms this global trend.

Some case reports and case series from developed world show that the underlying causes of PH in pregnancy are Group 1 PH, either idiopathic PAH or those associated with, for example, congenital heart disease (5). None of our patients had cause of PH other than either CHD or RHD. This could be because we looked only in at those with advanced disease and our case series could have missed other causes of PAH because we used only echocardiography to diagnose PH. We found a 19.1% overall maternal deaths (one of the four being a delayed maternal death occurring at four months), which is in the range of hat has been previously reported (17%–33%) mortality even though in these reports the patients had PH due to PAH (Group 1), as opposed to our series, which are in Group 2 PH (3).

Clinical worsening of PH during pregnancy has been reported to occur during late second trimester of pregnancy, when most physiologic hemodynamic changes occur (1,6,7). In our series, there were four cases of early deterioration; one at 19 and two at 26 weeks' of gestation, which is somewhat similar to previous reports. It has to be noted that most of our patients came late with advanced heart failure.

Although the initial pharmacologic management with pulmonary vasodilators like prostacyclin (epoprostenol) and prostacyclin analogues (iloprost, treprostinil), which are given via nebuliser or continuous subcutaneous or intravenous infusion, endothelin receptor antagonists (ERAs) bosentan, sitaxsentan, ambrisentan, and phos-phodiesterase-5 (PDE-5) inhibitors (sildenafil, tadalafil),which are administered orally, improve survival for patients with PAH by reducing RV afterload, none of the patients in this series were given these treatments (8,9). The only drug which is available in our setting is phosphodieterase-5 inhibitor, but we did not use this as most of our patients had Group 2 PH for which the dug is not useful or even be harmful (5).

Experiences with other ERAs and the PDE-5 show favourable functional and haemodynamic results in patients with PH associated with CHD and Eisenmenger syndrome, but we did not do right heart catheterization to evaluate the pulmonary vasoreactivity to diagnose eisenmenger physiology. The optimal time and mode of delivery remains debated; however, a recent study from a developed setting suggested that a planned cesarean section at 34 weeks was a preferred approach with good outcome after treatment for all women with nebulised targeted therapy at 8-34 weeks of gestation (9). In our setting if patients remained well, the pregnancy was allowed to continue until 39 weeks, considering the limited capacity of managing preterm neonates. Elective cesarean section has benefits where adequate staff is available (10). In our series, seven patients had scheduled cesarean delivery for cardiac indication.
The mode of delivery and anesthetic management of patients with severe PH is still controversial.

If vaginal delivery is chosen, low-dose epidural analgesia is thought to be beneficial (11,12). This has no considerable negative hemodynamic effect by itself, and it significantly decreases the adverse hemodynamic shift of labor (13). However, this requires continuous supply of epidural set and expertise, which makes it difficult to apply in low resource settings like ours. We did not have this service during the study period and four women in our series had instrument assisted vaginal delivery. There are now increasing number of reports highlighting the use of regional anesthesia for Cesarean section with better outcome (24). If epidural anesthesia is chosen, incremental dose epidural anesthesia is recommended to avoid rapid hemodynamic changes (12). Moreover, the use of single shot spinal anesthesia is contraindicated due to the potential hemodynamic compromise in PH (14).

The use of general anesthesia is also reported to have good maternal outcome (15,16). However, others have reported increased PAH during laryngoscopy and tracheal intubation and the side effect of positive-pressure ventilation on venous return may ultimately lead to cardiac decompensation (10,17). In our series, ten out of eleven patients took general anesthesia without notable complications and anesthetic drugs used included intravenous propofol, inhalational drugs like halothane for induction and analgesic drugs like phentanyl and morphine.

The postpartum period is a critical time for pregnant PH patients, because the risk of morbidity and mortality is greatest due to a marked increase in pulmonary vascular resistance and cardiac output (18). The majority of these hemodynamic changes resolve in the first two weeks after delivery with complete return to normal state over the subsequent six months (7). It is advocated that monitoring postpartum patients with PH in a critical care setting is required for several days (10). To ensure continued stability after delivery, 17 patients in our series were admitted to ICU. In the ICU patients, their hemodynamics were frequently followed clinically and by using non-invasive methods.

The cause of death among PH patients is not oftentimes clear, but right ventricular failure and ischemia, arrhythmias, and pulmonary embolism are likely mechanisms. In our series, one patient with membranous ventricular septa defect (VSD) died immediate post-partum. The second patient died four months post-partum of unexplained cause, and the third died after she was admitted with the diagnosis of NYHA class IV Heart failure, and community acquired pneumonia and progressive deterioration while on mechanical ventilator in the medical ICU. The fourth patient aborted in a health center and referred with NYHA class IV HF and died of possible massive pulmonary thromboembolism.

The leading cause of cardiovascular morbidity and mortality in Ethiopia is RHD, as is supported by some hospital and school based reports (20, 21). The risk of RHD is 1.6–2.0 times greater in women, which is likely to be due to several factors, including worsening of existing disease during pregnancy, group A β-hemolytic streptococcus (GAS) exposure during child rearing, limited access to services and intrinsic hormonal factors (26). This emphasizes on the need to give due attention to women in the prevention efforts of RHD. The average age of mortality due to RHD has been found to be 26.5 years; taking away the life of the young, most productive age group and women in their reproductive age group (22).

Our series also confirms that RHD is one of the causes of premature deaths in Ethiopia, in this case in pregnant mothers and hence a multidisciplinary team approach and early referral of cases to institutions better equipped to handle such cases is emphasized.

Limitations: We diagnosed PH based on clinical exams and tansthoracic echocardiography. Right heart catheterization with measurement of mean PAP and Pulmonary Capillary wedge pressure (PCWP) would have completed the standard definition of PH, and would have identified the dominant cause of PH. We studied cases of severe PH, despite which the proportion of was similar to other studies involving low risk cases with mild to moderate PH. The cause of death was not corroborated with postmortem findings and/or pathologic examination. The patients received diuretics, beta-blockers, anticoagulants and digoxin based on their NYHA functional class and hemodynamic status and the presence of atrial fibrillation at the discretion of the team, including a cardiologist, but we have not systematically analyzed the duration, the dose, routes of administration outcome for each therapy.

Conclusion: RHD still occurs among pregnant mothers in our setting.

We recommend a detailed and a well-designed evaluation involving a multi-disciplinary team with expertise in management of PH and high-risk obstetrics patients and including pre-conception counseling against pregnancy and possible early termination of pregnancy as well as options for permanent contraception. Prevention of RHD should be given due emphasis at the national level in order to avert the socio-economic burden the disease causes in the country.

Conflict of interest

Authors declare no conflict of interest.

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