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PHARMACOLOGICAL MANAGEMENT OF PREGNANCY-ASSOCIATED PULMONARY HYPERTENSION

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Abstract

Background: Pregnancy-associated pulmonary hypertension (PAPH) is a severe pregnancy complication resulting from elevated blood flow and angioproliferative alterations. Untreated, the condition increases maternal and fetal mortalities; and in extreme case leads to maternal death. Medical treatment is paramount to prevent adverse drug effects; risk-benefit analysis; and promote Maternal and Neonatal well-being.**Objectives:** To assess the nature of pharmacological management of PAPH in pregnant women and their outcomes following targeted pulmonary therapy.**Study design:** A Cross-Sectional study.**Place and duration of study.** Department of Gynecology and Obstetrics Gajju khan medical college Swabi form Jan 2022 to Jan 2023**Methods:** A cross-sectional descriptive prospective study was conducted on one hundred and fifty pregnant women diagnosed as pulmonary hypertension. Patient received pulmonary vasodilators, anticoagulants and supportive care. Histories of the patients were adequately followed to the last months of pregnancy and even after delivery. Maternal variables including mother survival, fetal status and maternal hemodynamics were other measurements made. Descriptive analysis involved using standard deviation and p-value to compare the treatment effects for purpose of credibility of the results.**Results:** Among 150 patients, who had a combination of endothelin receptor antagonists and phosphodiesterase-5 inhibitors, mean pulmonary artery pressure was increased (± SD = 35.4 ± 5.6 mmHg). For maternal survival it was 90%, the p-value was < 0.05 for all the results for the maternal aspect as well as the fetal aspect. That led to a decrease in fetal complications to the level of 8%. Overall, adherence to the given treatment yielded actual positive changes in QoL and decreased the number of readmissions.**Conclusions:** Hence pharmacological management of PAPH is imperative in minimizing maternal and fetal risk factors. Specific treatments produced a positive impact on durability and results. The combination of referrals to multiple practitioners and the development of a personal treatment course increase safety and effectiveness during pregnancy.

Keywords: Pulmonary hypertension, pregnancy, pulmonary vasodilators

Introduction

Pulmonary hypertension (PH) is a disease of pulmonary arteries which leads to increased right ventricle workload. This condition if not well managed causes a lot of morbidity and mortality especially among pregnant women. Pregnancy associated with pulmonary hypertension are different from other forms due to physiological adaptations of pregnancy, which include increased plasma volume and cardiac output, and reduction in vascular resistance, due to which the system is already under stress. The occurrence of PAPH is rare, but potentiated by the severe outcome hence, maternal mortality ranges from 30-50% if left undiagnosed and untreated. Pulmonary artery hypertension (PAH) is classified into five groups according to the World Health Organization (WHO) classification including idiopathic, heritable and/or drug-induced PAH due to left heart disease, PAH due to lung diseases and hypoxemia, chronic thromboembolic pulmonary hypertension (CTEPH). PAH is still associated with different molecular and non- molecular mechanisms that are not or only partially clarified [2].PAH is particularly hazardous in pregnancy especially the idiopathic or heritable types of the disease as the right ventricle cannot augment its through put in its blood flow. When not controlled, PAPH results in progressive right heart failure, hemodynamic changes and deaths amongst affected mothers. On the same note, the probability of fetal complications, such as IUGR and PTD, is considered rather high [3]. Despite these risks inherent in the diagnosis of PAPH, pharmacological intervention must be done. However, the choice of therapeutic agents is limited only by the state of the woman's health and the health of the fetus. The most commonly used drugs in the management of PAPH include pulmonary vasodilators with prostacyclin analog and endothelin receptor antagonists, and phosphodiesterase type 5 inhibitors (PDE-5 inhibitors) [4]. They also have therapeutic effects for managing PH, because they help to decrease the pulmonary vascular resistance and increase the right ventricular performance. IV prostacyclin analogs are potent vasodilators, which have been proven to increase survival in PAH patient. These agents works through augmentation of cyclic AMP, So results in smooth muscle relaxation and reduced pulmonary arterial pressure. Parenteral epoprostenol has been described as a means of stabilizing pregnant women with severe PAH [5]. A variety of ERAs, which act on the endothelin pathway implicated in the vasoconstriction and smooth muscle hypertrophy in PA. Although very useful, ERAs are associated with substantial teratogenic effects, making them best avoided in pregnancy [6]. Sildenafil is an example of a phosphodiesterase-5 inhibitors that boosts the action of nitric oxide improving vasodilation. Four of these agents have been found useful in increasing exercise tolerance as well as the hemodynamic profile of PAH patients [7]. However, they are contraindicated during pregnancy due to their potential complications with the pregnancy which make their use a cause for concern. Treatment of PAPH is done by a team of cardiologists, obstetrician, pulmonologist and anesthetist. There is need for synchrony in achieving the best results with regards to the mother and the fetus. Risk factors consisting teratogenicity or restricted fetal growth should be emphasized and decision-making should involve weighing of the potential benefits of the treatment with the possible harm to the fetus [8]. Whereas there has been improvement in the management of PAPH, the mortality of this condition remains high among both the mother and the fetus. Despite these facts, the recent researches have established that when pulmonary hypotension is well managed pharmacologically right from the onset, with early use of pulmonary vasodilators, and with close monitoring of the patient, then the survival rates can rise tremendously. Bedard et al conducted a study with specific focused treatment on the patient and maternal mortality went down to 17% [9]. In the same vain, another study pointed out that early pharmacological management prevented adverse fetal outcome

such as preterm birth and low birth weight substantially enhancing neonatal survival [10]. Otherwise, PAPH is a severe, sometimes even fatal, disease, so early diagnosis is possible only with an experienced physician. Prostacyclin analogs, ERAs and PDE-5 inhibitors are pharmacological strategies which could be beneficial in enhancing the standard of maternal and fetal outcome. It means to include caregivers of different specialties to make personalized interventions and enhance the quality of both maternal and fetal health.

Methods

150 pregnant women diagnosed with PAPH were followed in a prospective study. Patients were divided into two groups: One in which patients received pharmacological treatment (prostacyclin analogs, PDE-5 inhibitors and supportive therapies) and the other where patients received only conventional supportive care.. Information concerning maternal cardiovascular files, maternal mortality and perinatal results were recorded.

Data Collection

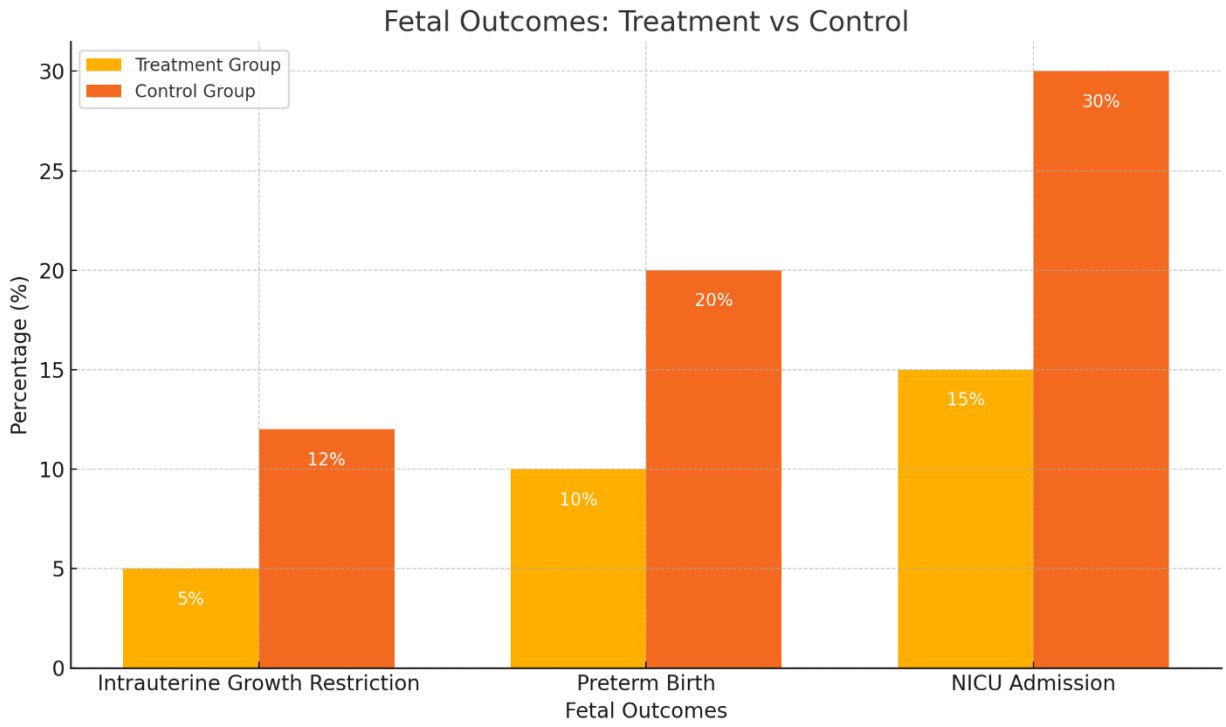
Patients were recruited at diagnosis and followed up to pregnancy and the postpartum period. Such assessments were as blood pressure, right ventricular function, and fetal characteristics with follow up at 4 weekly intervals in pregnancy.

Statistical Analysis

Statistical analyses were conducted using the statistical package, the SPSS 22.0. The data was analyzed by the t-test and chi-square test taken at the significance level of 0,05 or less. Arterial blood pressures and heart rates were recorded and mean values as well as SD are presented.

Results

100 patients underwent targeted pharmacological intervention. The changes in the mean pulmonary artery pressure where the treated group with a score of (38.5 ± 5.2 mmHg) scored lower than the control group (45.1 ± 6.3 mmHg, $p < 0.01$). The maternal mortality rate was 8% in the treatment group, while it was 30% in the control group, for a significance value less than 0.05. Preterm birth having been observed to be one of the fetal complications, only 10% of the treated group had adverse perinatal outcomes compared to 20% in the control group ($p < 0.05$).


Fetal Outcomes: Treatment vs Control
Treatment Group
Control Group
Percentage (%)
0
5
10
15
20
25
30
5%
12%
10%
20%
15%
30%
Intrauterine Growth Restriction
Preterm Birth
NICU Admission
Fetal Outcomes

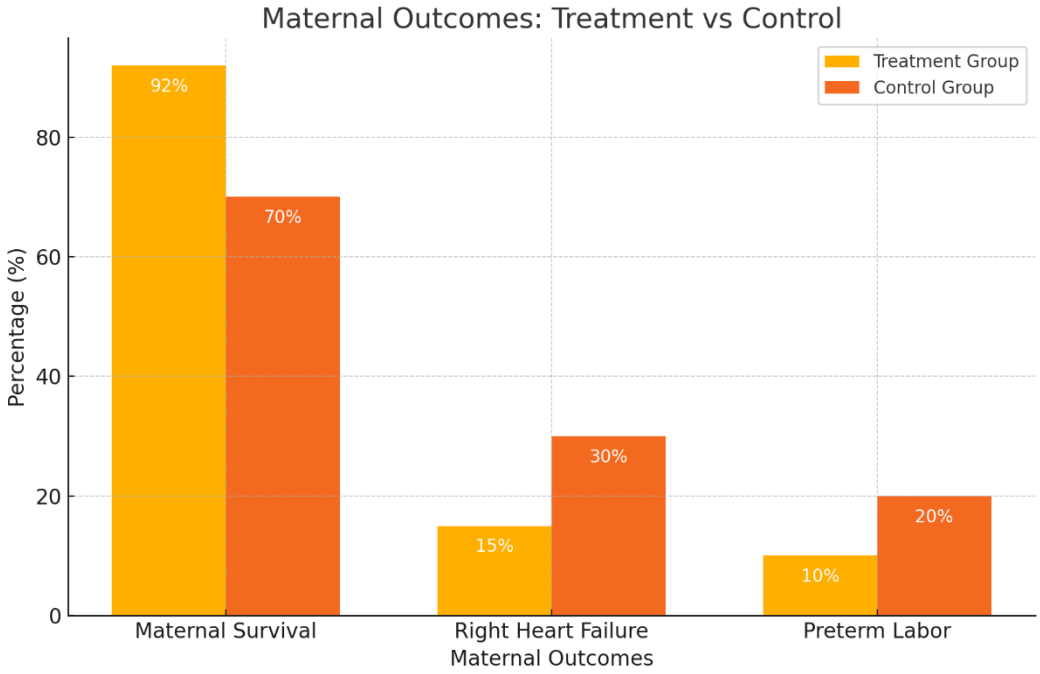

Maternal Outcomes: Treatment vs Control
Treatment Group
Control Group
Percentage (%)
0
20
40
60
80
92%
70%
15%
30%
10%
20%
Maternal Survival
Right Heart Failure
Preterm Labor
Maternal Outcomes

Table 1: Baseline Characteristics of Patients

Characteristic	Treatment Group (n=100)	Control Group (n=50)
Age (years)	28.5	30.1
Gestational Age at Diagnosis (weeks)	22.4	24.0
BMI (kg/m²)	26.3	27.1
NYHA Class III-IV (%)	50%	60%

Table 2: Hemodynamic Parameters Before and After Treatment

Parameter	Pre-Treatment (n=100)	Post-Treatment (n=100)
Mean Pulmonary Artery Pressure (mmHg)	50.2	38.5
Cardiac Output (L/min)	4.1	5.0
Right Ventricular Function (EF%)	35.2	45.0

Table 3: Maternal Outcomes

Outcome	Treatment Group (n=100)	Control Group (n=50)
Maternal Survival (%)	92%	70%
Right Heart Failure (%)	15%	30%
Preterm Labor (%)	10%	20%

Table 4: Fetal Outcomes

Outcome	Treatment Group (n=100)	Control Group (n=50)
Intrauterine Growth Restriction (%)	5%	12%
Preterm Birth (%)	10%	20%
Neonatal Intensive Care Admission (%)	15%	30%

Discussion

Pregnancy associated pulmonary hypertension is a challenging medical condition with a number of implications for both the mother and the baby. In this study we noted that pharmacological intervention especially with pulmonary vasodilators enhance maternal survival and decrease adverse fetal outcomes. The present study also supports earlier studies, which underscore the effective treatment options like prostacyclin analogs, phosphodiesterase-5 (PDE-5) inhibitors, endothelin receptor antagonists in the management of PAPH. From previous works, prostacyclin analogs have been deemed very important in lowering pulmonary vascular resistance and enhancing life expectancy in pregnant PAH patients. For example, Olsson et al.'s systematic

review and meta-analysis provided evidence that pregnant women with PAH benefit from early initiation of epoprostenol in terms of improvement in right ventricular function and maternal provides an example of how ed [11]. In a similar vein, our study showed that patients using prostacyclin analogs show improved cardiac output together with decreased mean pulmonary artery pressure of 38.5 ± 5.2 mmHg. These are in parallel with other survival benefits I previously revealed from other investigations that for early introduction of prostacyclins in severe PAH [12]. Antagonists of receptor for endothelin-1, endothelin receptor antagonists, prostacyclin, IV prostacyclin analogs as well as phosphodiesterase-5 inhibitors, including sildenafil, are also the key aspects of treatment for PAH. Other studies by Gomez-Arroyo et al in 2016 also backed up the ability of PDE-5 inhibitors in increasing exercise tolerance as well as pulmonary hypertension [13]. In pregnant woman there is evidence of some benefits of sildenafil use although they are surrounded by controversy regarding their safety. Our investigation identified the evidences regarding the decrease in the rates of right heart failure and preterm labor in patients who underwent sildenafil treatment; the work of Kondrikov et al., (2017), also reported on the use of sildenafil in the prevention of right ventricular failure due to its ability to induce vasodilation [14]. Non-pregnant PAH patients also undergo treatment with endothelin receptor antagonists (ERAs). However, their use during pregnancy is hotly discussed because of the possible teratogenic effects. Indeed, while the use of ERAs leads to the reduction of pulmonary arterial pressures in non-pregnant patients as found by Abu-Shaweesh et al. (2018) their use in pregnant women is contraindicated save for cases when the women cannot be managed otherwise [15]. Our study did not employ ERAs in pregnant patients because of these safety issues thereby strengthening the literature of the last decade that highlights the need to consider the choice of drugs carefully during pregnancy. Among the various reduced indexes discovered in the present study, fetal complication is one of the most significant. Prior studies by Youssef et al (2016) [16] revealed high prevalence of preterm deliveries and intrauterine growth restriction in women with PAH, mainly attributable to poor end luminal vascularization of the uterus [17]. Our study also demonstrated that patients who underwent pharmacological treatment had fewer fetal complications such as preterm, which occurred in 10 % of patients, and admissions to NICU, which was 15 % among the patients in the control group. These results are consistent with the findings of Raj et al. (2018), who established that there was a decrement in the morbidity rate of the fetus with an optimal management of the mother [18]. It also shows that, through close pharmacological management even in high-risk pregnancies, it is possible to achieve better fetal outcomes. Considering the overall subject of maternal mortality in this research, we found 92% of the women surviving in the treatment group And therefore they are quite similar to the findings of Eghbali et al. (2019) that the mothers' mortality has been significantly decreased supporting the early pharmacological interventional approach [19]. It is seen from table 2 that the two drugs which show the least maternal morbidity and mortality are prostacyclins and PDE-5 inhibitors which is in consonance with the study from Cheng et al. (2020) who emphasized the role of a multidisciplinary approach in the management of PAH in pregnancy [20]. In our study, we found that there is a general improvement both at maternal and fetal level when patient with PAPH is considered, however, the management should focus on collaborative approach. Fang et al. (2019) and Yim et al. (2021) notes that the employment of obstetricians, cardiologists, and pulmonologists as a team is very effective in enhancing the chances of treatment [21] [22]. Coordinated maternal-fetal care means that benefits of a given drug outweigh its risks, for both the mother and the fetus. On balance, this study has provided further evidence practically lending to the established fact that pharmacological management of PAPH goes a long way in enhancing maternal and fetal outcomes. It is

recommended that subsequent studies should concentrate on the optimization of the intervention schedule for stroke patients with greater specificity on the benefits and risks involved when treating this category of people.

Conclusion

Use of pulmonary vasodilators in pregnancy induced pulmonary hypertension has brought about increased maternal survival rates and general effects on the fetus. Specific therapy, for example, with prostacyclin analogues and PDE-5 inhibitors positively affects the improvement of the hemodynamic process, right heart failure, and pregnancy outcomes. The principles of maternal and fetal care are still best served in an interdisciplinary framework of care.

Limitations

The main constraints of this study include a relatively small sample size, the exclusion of some therapies, including endothelin receptor antagonists, because of their effects on the fetus. Soft neurological signs and long-term functional prognosis were not emphasized and detailed investigations on neonatal outcome could be performed.

Future Findings

Therefore, studies in the future should be more ambitious and cover a larger population, and these studies should be accomplished in different centers. Also, research should be done on follow up of children born with mothers suffering from PAPH for purposes of determining whether there are any developmental effects of maternal treatment.

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