***Manuscript title***

Pulmonary vasodilator therapy in preterm children with bronchopulmonary dysplasia; a nationwide study

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***Conflict of interest***

None

***Ethical statement***

The study was approved by an institutional review board, and consent was waived due to the registry study.

***Contributorship***

I.J., K.T.L. and E.N. contributed to planning the study. I.J., M.D., K.T.L. and E.N contributed to conducting the study. I.J., M.D., K.T.L and E.N. contributed to reporting the study.

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***Running title***

Pulmonary vasodilator therapy in preterm children

***Abstract***

*Objectives:* This study aimed to map prescription patterns of pulmonary vasodilator therapy in children with bronchopulmonary dysplasia (BPD).

*Working hypothesis:* Pulmonary vasodilator drug therapy is used in children born preterm suffering from BPD-associated pulmonary hypertension, but patient selection, extent of diagnostics with catheterization and co-morbidities are largely unknown.

*Study design:* A descriptive national registry-based study.

*Patient selection and methodology:* All children below seven years of age who had been prescribed a pulmonary vasodilator during a ten-year period, 2007-2017, born preterm (gestational age, GA <37 weeks) and classified as BPD, were included. Information on prescriptions was retrieved from the Swedish Prescribed Drug Register and information on patient characteristics and comorbidities was retrieved by linkage to national registers held by the National Board of Health and Welfare.

*Results:* In total, 74 children were included, 54 (73%) born at GA 22-27 and 20 (27%) at GA 28-36. Single therapy was most common, N=64 (86.5%), and sildenafil was most frequently prescribed, N=69 (93%). Bosentan, iloprost, macitentan and/or treprostinil were mainly used for combination therapies, N=10 (13.5%). Patent ductus arteriosus (PDA) or atrial septal defect (ASD) was present in N=29 (39%) and N=25 (34%) children respectively, and N=20 (69%) versus N=3 (12%) underwent closure. Cardiac catheterization was performed in N=19 (26%) patients. Median duration of therapy was 4.4 (0.5-14.1, 95% percentiles) months. Total mortality was N=7 (9%).

*Conclusions:* Preterm childrenwith BPD are prescribed pulmonary vasodilators, often without prior catheterization and sildenafil was most common. Diagnostic tools, effects, and drug safety needs further evaluation.

***Introduction***

Bronchopulmonary dysplasia (BPD), a pulmonary condition and developmental disease associated with premature birth, has been known since the 60s(1). Postnatal interventions such as mechanical ventilation, oxygen, surfactant, and systemic corticosteroids are lifesaving, but some may also lead to damage of the immature lung structures(2). BPD is currently considered to be caused by a combination of prenatal and postnatal factors, including a stunted development of the pulmonary circulation and decreased alveolarization(3, 4). Pulmonary hypertension (PH) may occur in 20-25% of preterm children diagnosed with BPD and is associated with an increased risk of morbidity and mortality(5-8). Mortality in BPD-PH has been described to be as high as 47% within two years following the PH diagnosis(9). The mechanisms of PH in BPD are not fully understood, but a vascular growth arrest in combination with hypoxemia has been suggested to increase vascular resistance (PVR), which with time may cause right heart failure(4).

The WHO 2018 classification of PH defines five main groups of PH and PH associated with BPD is categorized to subgroup three; PH due to lung disease and/or hypoxia(10-12). The European expert consensus document on diagnosis and treatment of pediatric PH was updated in 2019(13), and states that evidence is available for pulmonary vasodilator treatment in pediatric PAH, but conclusive treatment guidelines for BDP-PH are lacking and treatment decisions rely on expert opinions.

The aim of this study was to map nationwide prescription patterns of pulmonary vasodilator therapy among preterm children with BPD and to assess patient characteristics and comorbidities in these patients.

***Materials and Methods***

*Study population and data collection*

A nationwide study population was retrieved from the Swedish Prescribed Drug Register, including all children born in Sweden with at least one outpatient prescription of a pulmonary vasodilator at an age less than seven years during 2007-2017(14). Two authors (IJ and KTL) independently stratified these children according to the 2018 WHO classification of pulmonary hypertension(13). Preterm children with BPD (a subgroup within group 3 PH) were included in this current study. Further stratification into two groups based on gestational age at birth, 22-27 and 28-36 weeks respectively, was performed for further analysis. Perinatal information, morbidity and mortality data was retrieved for each included child.

*National registers*

The Swedish Prescribed Drug Register was established in 2005 and includes information on all prescribed drugs dispensed at pharmacies. Data on prescriptions with ATC codes that correspond to a pulmonary vasodilator was retrieved (sildenafil ATC G04BE03, tadalafil ATC G04BE08, bosentan ATC C02KX01, ambrisentan ATC C02KX02, iloprost ATC B01AC11, treprostinil ATC B01AC21, macitentan ATC C02KX04, riociguat ATC C02KX05, vardenafil ATC G04BE09, avanafil ATC G04BE10)(15). Data included information on dates for prescription and expedition, and concomitant drug treatments (diuretics, antacids, inhalants, and systemic steroids). Duration of pulmonary vasodilator treatment, stratified in this study to either more than one year or less, was obtained for all patients who received the first prescription of a pulmonary vasodilator prior to January 31st 2016.

The Swedish Medical Birth Register, established in 1973, contains data on 99% of all births and includes information on maternal medical history, pregnancy and delivery, as well as data of the newborn child. For this study, perinatal information on date of birth, gender, gestational age at birth, birth weight, and malformations were retrieved.

The Swedish National Patient Registercontains data on more than 99% of patients subjected to inpatient care and 80% of all hospital-based outpatient specialist care in Sweden. Retrieved data included information on diagnosis of pulmonary hypertension and possible comorbidities classified according to the International Statistical Classification of Diseases (ICD-10) and for further analyses ICD-10 codes I2, I31, I51, P05, P07.0-07.3, P22.1, P26-27, P29.3B, Q33, Q79.0, Q90, Q20-28, and I35 were used(16). Information on hospitalization and data on cardiac catheterizations (TFC10, TFC00) were also used. Hospitalization (days) after completed full term gestation and during the first year of life was used as a measure of morbidity.

Mortality data until the end of 2018 (date of death and cause of death) was retrieved from the Swedish Death Register, established in 1961.

All registries in this study are held by the Swedish National Board of Health and Welfare. A unique 12-digit national identification number is assigned to each resident in Sweden at birth and is used in all official population-based registries. This identification number makes linkage between the registers possible. Data was de-identified for the researchers.

***Statistical analysis***

Descriptive analyses were performed, and data are presented as number (N) and percentage (%) or median and 95% standard deviation (SD) as appropriate. IBM SPSS statistics Version 26 software was used for analysis.

***Results***

In total N=74 children with BPD met the inclusion criteria. Overall, the study included N=39 (53%) boys and N=35 (47%) girls. A majority, N=54 (73%), were born extremely preterm at a GA between 22-27 weeks, and N=20 (27%) were born at a GA between 28-36 weeks. Median birth weight was 625 grams (565-700) for children born at GA 22-27 and 1645 grams (1227-2095) for children born at GA 28-36. Overall, N=14 (19%) of the children were small for gestational age (SGA). Further demographic information is described in Table 1. Median hospitalization during the first year of life, after reaching full term, was 86 days (43-186). Down syndrome was present in two children, who were born at GA 28-36.

Sildenafil was the most used drug, prescribed to N=69 (93%) children, followed by bosentan to nine (12%) children, iloprost to seven (9%) children. Riociguat, macitentan and treprostinil were prescribed to one child each. No child was prescribed ambrisentan or tadalafil. Some children were prescribed more than one pulmonary vasodilator. Table 2 describes numbers and types of pulmonary vasodilators prescribed. Single pulmonary vasodilator therapy was most common, N=64 (86.5%). Ten children (13.5%) were prescribed two, three or at most five different types of pulmonary vasodilators, either in combination or as consecutive single therapies.

Median duration of pulmonary vasodilator drug therapy was 4.4 (0.5-14.1) months during the 10-year study period. A treatment duration of less than one year was most common, N=43 (68%), compared with N=20 (32%) children with a treatment duration of more than one year.

Concomitant drug therapies were common, and most children received additional treatment with antacids; N=39 (53%), inhalants; N=67 (91%), diuretics; N=52 (70%) and/or systemic steroids; N=16 (22%).

Age at first outpatient prescription is shown in Figure 1. Most patients were young, a median age of 7 months (5-10.25) or 3 months (1.75-6.25) when corrected for GA. N=37 (52%), were prescribed a pulmonary vasodilator within the first month after neonatal hospitalization.

A patent ductus arteriosus (PDA) was present in a total of N=29 (39%) children and of these N=20 needed a PDA closure, either with device or surgery as described in table 3. Fifteen (75%) of these children were less than one year of age at the time of closure and in N=12 (60%) the PDA was closed prior to the first pulmonary vasodilator prescription. An atrial septal defect (ASD) was present in N=25 (34%) children and of these three (12%) underwent device closure. In two (67%) children the ASD was closed at less than one year of age and prior to the first pulmonary vasodilator prescription. Some of the children (N=15) had an ASD and a PDA. In total N=14 (19%) of all children, regardless of a PDA and/or an ASD, had concomitant heart disease; non-ductal dependent congenital heart defect (CHD) (12/14), cardiomyopathy (1/14) or arrythmia (1/14). Cardiac catheterizations had been performed in N=19 (26%) children, of which N=14 procedures included a device closure.

Mortality rates are described in Figure 2. Seven patients (9%) died during the study period; four born at GA 22-27 and three born at GA 28-36, as described in table 4. Most patients, N=5 (71%), were older than one year of age at the time of death. Single use of pulmonary vasodilator therapy was most common among these patients, N=5. Five patients were considered to have a pulmonary underlying cause of death and the remaining two had another cause of death, not primarily related to pulmonary vascular disease.

***Discussion***

This nationwide register-based study describes all prescriptions of pulmonary vasodilator drugs to preterm children with BPD during a 10-year period and provides a different perspective compared to previous studies of BPD-PH. Current treatment guidelines are to a large extent based on expert opinion and more knowledge is needed.

*BPD and incidence*

BPD is defined as mild, moderate, or severe and recent studies have updated the definition to include mode of ventilatory support at 36 weeks of GA, regardless of supplemental oxygen(17). The incidence of BPD among preterm children seems to have been stable over the years, but with very uncertain numbers, ranging from 17-75%(18). A stable incidence can likely be explained by a combination of improved neonatal intensive care, with less lung injuries, in parallel with increased survival rates among the children born extremely preterm(2, 19). During the study period just below 400 children in Sweden were diagnosed with BPD(14). Based on our data we assume that 20% of them were treated with a pulmonary vasodilator drug. After premature birth there is a well-known increased risk of PH related to the severity of BPD(7). Previous studies have reported the incidence of PH in BPD as 18 to 42%, and as much as 60 to 80% among extremely preterm children (GA 22-27)(5, 6). A majority of the treated children in our study (N=54, 73%) were extremely preterm, in line with previous studies of incidence of PH.

*Pulmonary vasodilator therapy*

Sildenafil was the most used vasodilator drug in this study. Sildenafil is also the most studied pulmonary vasodilator for children, but the pharmacodynamics and impact on BPD-PH has not been sufficiently evaluated(13). Bosentan was also used to some extent in our study, but newer pulmonary vasodilators only in sporadic cases. The mechanisms of PH in BPD are multifactorial. Stunted pulmonary development with decreased alveolarization and vascular growth, resulting in a hypoplastic pulmonary vascular bed, may have an impact, but other factors such as open fetal shunts may contribute(3, 4). A positive effect on growth of the pulmonary vascular tree with use of vasodilators has been demonstrated in fetal animal studies but has, to our knowledge, not yet been demonstrated in humans(20). One can speculate that children in our study, who had undergone a catheterization, showed some degree of reactivity to oxygen and/or nitric oxide which made it reasonable for the treating physician to try a pulmonary vasodilator drug. However, many had not undergone a catheterization and the decision to treat was likely based on other parameters. Improvement of clinical and hemodynamic parameters have previously been reported for pulmonary vasodilator therapy in BPD-PH(21). Additional efficacy and safety studies of vasodilator therapy in premature children with BPD-PH are needed.

The median age at first prescription was 7 months (3 months when adjusted for prematurity). Four children were prescribed a vasodilator prior to reaching full term and even fewer had the first prescription after one year of age. This study includes pulmonary vasodilator prescriptions following discharge from hospital, and it is likely that many treatments were initiated during the time in hospital. Therefore, the median age for start of therapy may be even lower than what the prescription age indicates. Optimal start time and risks associated with discontinuation of BPD-PH vasodilator therapy are still unknown.

Studies on pharmacokinetics in children born preterm are sparse. In general, sildenafil is considered safe for long-term (one year) use with few side effects in children less than 2 years of age (22). However, adverse events have been reported, including severe hypoxia (possibly caused by increased intrapulmonary shunting or ventilation-perfusion mismatch), aggravated gastroesophageal reflux and retinopathy, and treatment should therefore be prescribed with caution (23-25). Most children in our study were treated for less than a year (68%). The reason for this is not known, but factors as spontaneous pulmonary vascular growth or improved saturations from vasodilator therapy may contribute. Information on adverse events was not included in the register and could therefore not be retrieved.

*Diagnostics of BPD-PH*

PH is defined as a mean pulmonary arterial pressure above 20-25 mmHg for children beyond three months of age(12). Consensus is lacking whether chronological or corrected age should be used for this definition in preterm children(26). Diagnosis should ideally be confirmed by cardiac catheterization, especially before adding a second pulmonary vasodilator, but this is still seldom done(13, 27-29). Only five children in this study underwent a purely diagnostic right heart catheterization prior to vasodilator treatment. BPD-PH in children born preterm probably develops at an early stage and echocardiographic signs of PH have been described in 42% of children born preterm (median 27 weeks GA at birth) at an age of seven days(5). Echocardiography is today the standard method used to evaluate and diagnose PH in preterm children and it is recommended to screen for PH at the time of BPD diagnosis or if supplemental oxygen is needed at a gestational age of 34−36 weeks(13). Considering the overall morbidity of these children it may be reasonable, and an advantage, to use only echocardiography to monitor and evaluate vasodilator therapy. Echocardiography is easily accessible, and without risks.

*PDA and/or ASD interventions*

The incidence of PDA and ASD in preterm children varies between studies and depends on diagnostic criteria, age and birth weight of the studied population(30, 31). In this study a total of 29 (39%) children were diagnosed with PDA (without a ductal dependent CHD) and 25 (34%) with ASD. Of these, 31 (57%) were not closed during the study period and 9 (17%) were closed after the initiation of vasodilator therapy. PDA, as well as ASD, is associated with an increased risk of necrotizing enterocolitis, intraventricular hemorrhage, and BPD in children born preterm(32). The benefit of an early PDA closure has been debated, and a recent study of modern neonatal care has not confirmed a previously demonstrated gain(33). There is still support for PDA closure in children with clear symptoms and hemodynamically significant shunts(34). The impact of PDA and/or ASD on the development of PH in preterm children is not known. An increased pulmonary blood flow in preterm children with open ASD shunts has been shown to increase the risk of PH(35). PDA is not considered a major risk factor for BPD-PH, but the current practice, where centers tend to wait for the PDA to close spontaneously, needs to be evaluated in relation to PH development and risk(36, 37).

*Mortality*

BPD-PH mortality has been reported to exceed 40% within two years from diagnosis, and often occurs during the first 6 months of life(9). The premature children included in our study survived the first period of neonatal intensive care, were discharged, and were prescribed vasodilator drug therapy outside of hospital. 9% of the children died during the study period. Mortality rates of discharged children treated for BPD-PH have to our knowledge not been studied previously.

*Limitations*

The Swedish registers are standardized and include prospectively obtained data on birth, drugs, and diseases of the child with high specificity. Data was de-identified for the researchers and retrieved in a uniform way which limited the risk of selection bias. However, as most register-based studies, this study is retrospective which may introduce a risk of misclassification and selection bias. Two researchers (KTL and IJ) individually categorized the included ICD codes in the large data base to WHO PH-group classification, to include only BPD-PH cases in this study. The children were equally classified by the researchers, which limit the risk of misclassification. All national registers used for this study are validated, with good coherence between the registries and medical records, and the risk of selection bias is thereby reduced.

*Conclusion*

In conclusion, sildenafil was the most prescribed pulmonary vasodilator drug in preterm children with BPD in Sweden. Treatment was usually initiated within the first few months of life without a prior diagnostic catheterization and the duration of treatment was most often less than one year. An open PDA and/or ASD was common.

The pathophysiology of BPD-PH in preterm children is not fully understood. The impact of vasodilator therapy, as well as timing, duration, and long-term effects needs further evaluation.

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***References***

1. Northway WH, Jr., Rosan RC, Porter DY. Pulmonary disease following respirator therapy of hyaline-membrane disease. Bronchopulmonary dysplasia. N Engl J Med. 1967;276(7):357-68.

2. Thebaud B, Goss KN, Laughon M, Whitsett JA, Abman SH, Steinhorn RH, et al. Bronchopulmonary dysplasia. Nat Rev Dis Primers. 2019;5(1):78.

3. Day CL, Ryan RM. Bronchopulmonary dysplasia: new becomes old again! Pediatr Res. 2017;81(1-2):210-3.

4. Lignelli E, Palumbo F, Myti D, Morty RE. Recent advances in our understanding of the mechanisms of lung alveolarization and bronchopulmonary dysplasia. Am J Physiol Lung Cell Mol Physiol. 2019;317(6):L832-L87.

5. Mourani PM, Sontag MK, Younoszai A, Miller JI, Kinsella JP, Baker CD, et al. Early pulmonary vascular disease in preterm infants at risk for bronchopulmonary dysplasia. Am J Respir Crit Care Med. 2015;191(1):87-95.

6. Weismann CG, Asnes JD, Bazzy-Asaad A, Tolomeo C, Ehrenkranz RA, Bizzarro MJ. Pulmonary hypertension in preterm infants: results of a prospective screening program. J Perinatol. 2017;37(5):572-7.

7. Arjaans S, Zwart EAH, Ploegstra MJ, Bos AF, Kooi EMW, Hillege HL, et al. Identification of gaps in the current knowledge on pulmonary hypertension in extremely preterm infants: A systematic review and meta-analysis. Paediatr Perinat Epidemiol. 2018;32(3):258-67.

8. Naumburg E, Soderstrom L, Huber D, Axelsson I. Risk factors for pulmonary arterial hypertension in children and young adults. Pediatric pulmonology. 2016.

9. Khemani E, McElhinney DB, Rhein L, Andrade O, Lacro RV, Thomas KC, et al. Pulmonary artery hypertension in formerly premature infants with bronchopulmonary dysplasia: clinical features and outcomes in the surfactant era. Pediatrics. 2007;120(6):1260-9.

10. Simonneau G, Gatzoulis MA, Adatia I, Celermajer D, Denton C, Ghofrani A, et al. Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol. 2013;62(25 Suppl):D34-41.

11. Rosenzweig EB, Abman SH, Adatia I, Beghetti M, Bonnet D, Haworth S, et al. Paediatric pulmonary arterial hypertension: updates on definition, classification, diagnostics and management. European Respiratory Journal. 2019;53(1).

12. Simonneau G, Montani D, Celermajer DS, Denton CP, Gatzoulis MA, Krowka M, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J. 2019;53(1).

13. Hansmann G, Koestenberger M, Alastalo T-P, Apitz C, Austin ED, Bonnet D, et al. 2019 updated consensus statement on the diagnosis and treatment of pediatric pulmonary hypertension: The European Pediatric Pulmonary Vascular Disease Network (EPPVDN), endorsed by AEPC, ESPR and ISHLT. The Journal of Heart and Lung Transplantation. 2019;38(9):879-901.

14. <https://www.socialstyrelsen.se/en/statistics-and-data/registers/> [

15. <https://www.whocc.no/atc/structure_and_principles/> [

16. <https://www.who.int/standards/classifications/classification-of-diseases> [

17. Jensen EA, Dysart K, Gantz MG, McDonald S, Bamat NA, Keszler M, et al. The Diagnosis of Bronchopulmonary Dysplasia in Very Preterm Infants. An Evidence-based Approach. Am J Respir Crit Care Med. 2019;200(6):751-9.

18. Siffel C, Kistler KD, Lewis JFM, Sarda SP. Global incidence of bronchopulmonary dysplasia among extremely preterm infants: a systematic literature review. J Matern Fetal Neonatal Med. 2021;34(11):1721-31.

19. Stoll BJ, Hansen NI, Bell EF, Walsh MC, Carlo WA, Shankaran S, et al. Trends in Care Practices, Morbidity, and Mortality of Extremely Preterm Neonates, 1993-2012. JAMA. 2015;314(10):1039-51.

20. Ladha F, Bonnet S, Eaton F, Hashimoto K, Korbutt G, Thebaud B. Sildenafil improves alveolar growth and pulmonary hypertension in hyperoxia-induced lung injury. Am J Respir Crit Care Med. 2005;172(6):750-6.

21. Kadmon G, Schiller O, Dagan T, Bruckheimer E, Birk E, Schonfeld T. Pulmonary hypertension specific treatment in infants with bronchopulmonary dysplasia. Pediatric pulmonology. 2017;52(1):77-83.

22. Mourani PM, Sontag MK, Ivy DD, Abman SH. Effects of long-term sildenafil treatment for pulmonary hypertension in infants with chronic lung disease. J Pediatr. 2009;154(3):379-84, 84 e1-2.

23. Fang AY, Guy KJ, Konig K. The effect of sildenafil on retinopathy of prematurity in very preterm infants. J Perinatol. 2013;33(3):218-21.

24. Bhatt-Mehta V, Donn SM. Sildenafil for pulmonary hypertension complicating bronchopulmonary dysplasia. Expert Rev Clin Pharmacol. 2014;7(4):393-5.

25. del Cerro MJ, Sabate Rotes A, Carton A, Deiros L, Bret M, Cordeiro M, et al. Pulmonary hypertension in bronchopulmonary dysplasia: clinical findings, cardiovascular anomalies and outcomes. Pediatric pulmonology. 2014;49(1):49-59.

26. Hansmann G, Sallmon H, Roehr CC, Kourembanas S, Austin ED, Koestenberger M, et al. Pulmonary hypertension in bronchopulmonary dysplasia. Pediatr Res. 2021;89(3):446-55.

27. Apitz C, Hansmann G, Schranz D. Hemodynamic assessment and acute pulmonary vasoreactivity testing in the evaluation of children with pulmonary vascular disease. Expert consensus statement on the diagnosis and treatment of paediatric pulmonary hypertension. The European Paediatric Pulmonary Vascular Disease Network, endorsed by ISHLT and DGPK. Heart. 2016;102 Suppl 2:ii23-9.

28. Krishnan U, Feinstein JA, Adatia I, Austin ED, Mullen MP, Hopper RK, et al. Evaluation and Management of Pulmonary Hypertension in Children with Bronchopulmonary Dysplasia. J Pediatr. 2017;188:24-34 e1.

29. Malloy KW, Austin ED. Pulmonary hypertension in the child with bronchopulmonary dysplasia. Pediatric pulmonology. 2021;56(11):3546-56.

30. Leirgul E, Fomina T, Brodwall K, Greve G, Holmstrom H, Vollset SE, et al. Birth prevalence of congenital heart defects in Norway 1994-2009--a nationwide study. American heart journal. 2014;168(6):956-64.

31. Dice JB, J. Patent Ductus Arteriosus: An Overview. J Pediatr Pharmacol Ther. 2007;12:138-46.

32. Mitra S, Scrivens A, von Kursell AM, Disher T. Early treatment versus expectant management of hemodynamically significant patent ductus arteriosus for preterm infants. The Cochrane database of systematic reviews. 2020;12:Cd013278.

33. Sung SI, Chang YS, Chun JY, Yoon SA, Yoo HS, Ahn SY, et al. Mandatory Closure Versus Nonintervention for Patent Ductus Arteriosus in Very Preterm Infants. J Pediatr. 2016;177:66-71 e1.

34. Sankar MN, Bhombal S, Benitz WE. PDA: To treat or not to treat. Congenital heart disease. 2019;14(1):46-51.

35. Vyas-Read S, Guglani L, Shankar P, Travers C, Kanaan U. Atrial Septal Defects Accelerate Pulmonary Hypertension Diagnoses in Premature Infants. Front Pediatr. 2018;6:342.

36. Nagiub M, Kanaan U, Simon D, Guglani L. Risk Factors for Development of Pulmonary Hypertension in Infants with Bronchopulmonary Dysplasia: Systematic Review and Meta-Analysis. Paediatric respiratory reviews. 2017;23:27-32.

37. Sheth S, Goto L, Bhandari V, Abraham B, Mowes A. Factors associated with development of early and late pulmonary hypertension in preterm infants with bronchopulmonary dysplasia. J Perinatol. 2020;40(1):138-48.