Journal of Cardiovascular Disease Research

ISSN: 0975-3583,0976-2833 VOL13,ISSUE05,2022

Eisenmenger Syndrome: an overview and India Perspective

Dr.Prashanth RM*, Dr. Hrishikesh Rangnekar**

*Associate Professor, Dept. of Cardiology, Yenepoya Medical College, Deralakatte, Mangalore, Karnataka

**Professor, Dept. of Swasthavritta, Pt. Dr.ShivshaktiLal Sharma Ayurved Medical College, Ratlam, Madhya Pradesh

Abstract

Eisenmenger syndrome (ES) is chronic systemic hypoxemia caused by reversalshunt from an unrepaired acyanoticcongenital heart disease (CHD) and due to increased pulmonary vascular resistance (PVR). In today's medically advanced era also ES needs to be discussed, as there is no single drug that tackles the PVR or reverses the shunt. Country like India has various issues in tackling the ES. There needs to be thoughtful strategy in every aspect of the ES, starting from screening, diagnosing, treating ES, so that quality of life of ES patients becomes better.

Historical background

It was way back in 1897 that Victor Eisenmenger described a 32 year old case, an obese man having a history of dyspnea and cyanosis from infancy who succumbed to a massive hemoptysis[1]. After the autopsy, he was found to have a large ventricular septal defect with an overriding aorta. This was then known as Eisenmenger complex, however, it was much later, in 1958 Paul Wood coined this term 'Eisenmenger syndrome'[2], which essentially included increased pulmonary vascular resistance (PVR).

The Eisenmenger syndrome represents an advanced stage of a spectrum of structural and functional changes in the pulmonary vasculature which lead to a progressive increase in pulmonary vascular resistance[3].

Definition

Paul Wood defined ES as "pulmonary hypertension at systemic level, due to a high pulmonary vascular resistance (over 800 dynes sec./cm.), with reversed or bidirectional shunt" leading to systemic hypoxemia and cyanosis in persons with ACHDii. Includes all large intra- and extra-cardiac defects which begin as systemic-to-pulmonary shunts and progress with time to severe elevation of PVR and to reversal (pulmonary-to-systemic) or bidirectional shunting; cyanosis, secondary erythrocytosis, and multiple organ involvement are usually present[4]

Epidemiology andPathophysiology

Nowadays, early diagnosis and timely repair of CHD often prevent the development of ES. In economically developed countries, incidence of ES has decreased over time. Patients with post-tricuspid shunts usually develop ES early during infancy or childhood and account for the majority of patients with ES. Those with a pre-tricuspid shunt tolerate the increase in pulmonary blood flow much better than patients with post-tricuspid shunts, and only a few with unrepaired shunt develops ES[5,6]

Prevalence of ES in underdeveloped / developing nations is more compared to the developed nations, due to various reasons including paucity of cardiac surgery to the child having congenital heart disease (CHD)[7]. Also, various congenital conditions like Trisomy 21, thoracic and spinal skeletal deformities; and lung parenchymal disease are often associated with a higher likelihood of developing pulmonary vascular disease[3].

ISSN: 0975-3583,0976-2833 VOL13,ISSUE05,2022

Eisenmenger syndrome develops due to long standing, non-treated intracardiac defects like atrial septal defect (ASD), ventricular septal defect (VSD), single ventricle with unobstructed pulmonary blood flow, and extracardiac shunts like truncus arteriosus and patent ductus arteriosus. All such birth defects lead to left to right shunt and an obvious increase in pulmonary blood flow. During initial years however, such shunts are usually small or even absent because of the high PVR. Gradually, over years of such left-to-right shunt, and by continuous increased blood flow, pulmonary endothelium remodelling occurs after endothelial dysfunction. This is fuelled by media hypertrophy of the small arteries, intima proliferation leading to pulmonary arterial hypertension (PAH). Many factors such as duration and quantum of left to right shunt decide the pace of this disease progression. Shunts at the level of ventricles or great arteries (post-tricuspid) are responsible for fast progression of the disease than that at atrial (pre-tricuspid) level.

Over years, in progressed stage, as the disruption of the vessel wall peaks, it is exhibited in a variety of deformities such as plexiform lesions, arteritis, fibrosis. The lumen of the pulmonary artery gets compromised due to obstructions further increasing the mean pulmonary arterial pressure (mPAP), worsening the PAH[8]. Flow is reversed once the pulmonary arterial pressure exceeds the systemic pressure. This is the classical pathology of ES and at this stage hypoxemia and central cyanosis is seen.

Clinical Presentation

In clinical studies of ES, WHO functional class is considered to know the severity of pulmonary hypertension, in which dyspnea on exertion (exercise intolerance) is seen. Due to this, patients resort to lesser physical activities and lifestyle, thereby underestimating the symptoms[9]. Fatigue, endocarditis, brain abscess and syncope are common findings. Multiple systems are involved in ES due to chronic hypoxemia, erythrocytosis and heart failure. Chest pain, cyanosis, hemoptysis are also relatively common. Long standing cyanosis, increasing arterial desaturationand secondary polycythemiaaffects multiple organs with increased morbidity and hospitalisations and it hampers overall quality of life[10]. The symptoms and sicknesses include cerebral abscess, syncope, right ventricular hypertrophy, congestive heart failure, dysrhythmia, diffuse joint and long bone pains from hypertrophic osteoarthropathy, excess bleeding with trauma, GI bleeding, headaches, gout,cholelithiasis,infected hypertrophied gums etc. Of particular importance,renal function is impaired in adult congenital heart disease (ACHD) patients. In a large cohort of such patients, about twothirds of patients with ES had impaired renal functions is associated with worse survival[11].

On physical examination one may feel theprominent pulmonary arterial pulsations, loud pulmonary component of the second heart sound, right ventricular heave and, frequently, an early diastolic murmur (of pulmonary regurgitation).Central cyanosis is evident along with clubbing. Patients may suffer from arrhythmic events (especially supraventricular arrhythmias), heart failure (HF) and sudden cardiac death[12]. At the later stage of the disease, cardiac output may drop considerably with severe cyanosis. Due to persistent hypoxemia, secondary erythrocytosis sets in further leading to iron deficiency (leading to anemia; even inapt phlebotomies are the cause of anemia[13]) and increased blood viscosity. These abnormalities make ES patients vulnerable to bleeding and thrombosis leading to recurrent hemoptysis and even in-situ pulmonary artery thrombosis.

Diagnostic and Prognostic tools

In the Paul Wood paper in BMJ in 1958, he mentioned the ES associated anomalies. Almost 5% of patients with congenital heart disease had one more family member suffering from same condition. Limb deformities were associated in the majority of the VSD patients; maternal rubella, cataract, deafness favoured patent ductus.

ISSN: 0975-3583,0976-2833 VOL13,ISSUE05,2022

For the confirmed diagnosis of ES (with appropriate medical history), Transthoracic echocardiography (TTE) is by far the best tool. TTE gives a complete picture starting from the structural defect to direction of the shunt. It also allows estimating pulmonary artery pressures with the modified Bernoulli equation via pulmonary or tricuspid regurgitation[14].

Patient with an unattendedcongenital heart disease such as ASD,VSD, PDA etc. visiting the hospital with complaintssuch as effort intolerance / diminished physical activities, fatigue, cyanosis should be considered for diagnosing ES. Patients with post-tricuspid shunts have fast progression of the disease and diagnosis of such patients happenmostly before their adulthood.

An episode of pulmonary haemorrhage is typically the characteristic of rapid progression of the disease. Among patients with ES, advanced heart failure is reported as the most common cause of death, followed by infections, arrhythmia or sudden cardiac death[15]. According to other publication, congestive heart failure, massive hemoptysis, or thromboembolism are the common causes of death[16].

Idiopathic PAH, PAH with systemic to pulmonary shunt and segmental PAH can be considered in the differential diagnosis of ES.

One multi-centric, cross-sectional APPROACH-IS (Assessment of Patterns of PatientReported Outcome [PRO] in Adults with CHD International Study) revealed that the patients with cyanotic heart disease or ES had the worst physical function, mental health, and quality-of-life compared with individuals with other types of CHD[17].

In their original article entitled ‘Advanced pulmonary vascular disease: the Eisenmenger syndrome’, R. Krishna Kumar and Julio Sandoval proposed following diagnostic approach to patients with suspected Eisenmenger syndrome:

Investigation	**Rationale**	**Recommendations**
Measurement of oxygen saturation	Assessment of severity of hypoxemia	At initial evaluation and on follow-up
Arterial blood gas	An elevated PCO2 may suggest underlying lung disease	When impaired lung function is suspected (i.e., patients with spinal skeletal deformities and upper airway obstruction)
Chest X-ray	Analysis of the cardiac size and chambers as well as the lung fields is crucial for a preliminary understanding of cardiac remodeling and associated (respiratory) disorders	At initial evaluation and on follow-up if clinically indicated
Pulmonary function tests	Impaired lung function can substantially elevate pulmonary vascular resistance and contribute to hypoxia	Clinical suspicion of lung disease, spinal skeletal deformities, airway obstruction merit thorough evaluation of lung function
Electrocardiogram	Allows identification of chamber enlargement and underlying rhythm. Atrial flutter is common in these patients	At initial evaluation and on follow-up
Trans-thoracic echocardiography	Complete diagnosis of the underlying congenital cardiac defect, assessment of pulmonary artery systolic pressure, assessment of ventricular function and competence of valves	At initial evaluation and follow-up when indicated

ISSN: 0975-3583,0976-2833 VOL13,ISSUE05,2022

Trans-esophageal echocardiography	Provides a consistently better quality of imaging, and is of particular value in patients with poor transthoracic windows	Patients with unsatisfactory trans-thoracic images because of limited windows
Six-minute walk test	Simple, inexpensive and reproducible measure of functional capacity. Demonstrated prognostic value in idiopathic pulmonary arterial hypertension	At baseline and during follow-up
Formal exercise testing with measurement of oxygen consumption	Oxygen consumption of ,10.4 ml/min/m2 is associated with poor prognosis in idiopathic pulmonary arterial hypertension	Not routinely recommended. May be warranted as clinical trial end point
Cardiac catheterization and angiography	Measurement of pulmonary arterial pressures and vascular resistance; assessment of response to vasodilators. Analysis of the capillary network and proximal arteries and veins (thrombotic lesions and stenoses)	Routine catheterization may be unnecessary in advanced Eisenmenger syndrome if noninvasive evaluation provides adequate information for therapeutic decisions
Magnetic resonance imaging	High quality anatomic definition, assessment of ventricular function, estimation of flows andresistances	Cost and lack of expertise limits its application in those regions where advanced disease is most prevalent. It has the potential to completely replace cardiac catheterization in some cases, in centers where expertise on magnetic resonance imaging is available
Chest computed tomography	Allows identification of intrapulmonary thrombi ,assessment of branch pulmonary arteries, pulmonary veins and lung parenchyma with great accuracy and clarity	Requires less expertise than magnetic resonance imaging
Complete blood counts	Hemoglobin and hematocrit estimation, mean corpuscular volume and mean corpuscular hemoglobin concentration	At baseline and on follow up
Serum ferretin and transferring saturation	Routine complete blood counts may not provide any clues about iron deficiency	In all patients with significant hypoxemia (resting saturations ,90%) and in all patients with erythrocytosis
Liver and renal function tests, serum uric acid	To evaluate commonly affected organs. Renal dysfunction is particularly common with advancing disease	At baseline and during follow up

Management of ES

Periodic assessment and counselling of all aspects of the disease is important in the management of ES[18]. Corrective surgery after the well-established ES is contraindicated for the perioperative risk and high possibility of adverse outcome[19]. Conservative treatments and targeted PAH therapies are the effective options. Arrhythmias should be managed proactively as they are major cause of morbidity and mortality. Lung transplantation with defect correction or heart-lung transplantation are the last resort for patients failing the pharmacotherapy, however paucity of donors is challenging. Even though both veno-arterial extracorporeal membrane oxygenation (ECMO) and ventricular assist devices have not been well documented; mechanical circulatory support can be used as a bridge to transplantation strategy for patients with end-stage ES[20].

ISSN: 0975-3583,0976-2833 VOL13,ISSUE05,2022

Due to pulmonary endothelial dysfunction, production of vasodilators like nitric oxide and prostacyclins are declined whereas there is an overexpression of vasoconstrictors like endothelin 1[21]. There is a need for selective pulmonary vasodilators for treating ES, as drugs with systemic vasodilator effect may increase the right to left shunt thereby further worsening cyanosis[22].Bosentan (dual endothelin receptor antagonist) and sildenafil (PDE-5 inhibitor) are studied in ES through randomized controlled trials.

Iron deficiency should be tackled with intravenous iron supplements,sinus rhythm should be restored and adequate hydration is an important factor in the management of ES. ACE inhibitors or angiotensin receptor blockers do not improve survival. Digoxin seems to increase mortality while beta-blockers may have a positive impact on survival[23].

Radiofrequency ablation is recommended as an alternative approach for supraventricular tachycardias[24]. Epicardial pacemakers and leadless implantable cardioverter defibrillators are to be used to minimise thromboembolic events. Anticoagulation (especially vitamin K antagonists) is recommended only in patients with atrial flutter or fibrillation, frequent thromboembolisms, pulmonary artery thrombosis with no or minimal hemoptysis and mechanical prosthetic valve[25].

Cardiovascular risk factors should be kept in check and smoking cessation is strongly recommended. Current European Society of Cardiology (ESC) guidelines on ACHD recommend the initiation of an ERA (endothelin receptor antagonist) monotherapy in patients with reduced exercise capacity (6 Minute Walking Distance: 6MWD)[26]

ES and Pregnancy

Pregnancy in women with pulmonary vasculopathies is rare, with an incidence estimated at 1.1 per 100 000 pregnancies.[27] Women with PH tolerate haemodynamic changes of pregnancy poorly, which results in deterioration leading to maternal/fetal demise. Mortality rates reported in the literature vary between 30 and 56%.[28] There is an increased risk of preterm birth and fetal growth restriction, in addition to the increased risk of perinatal mortality[29]

Current guidelines clearly recommend the avoidance of pregnancy in women with PAH and termination when pregnancy does occur.[30] This recommendation is of particular significance given that PAH often affects women of childbearing age.[31]

The causes of poor maternal outcomes are varied and include risk of death from right heart failure and stroke from intracardiac shunting.[32] There is a high peri-/post-partum risk due to haemodynamic stress, bleeding complications and the use of general anaesthesia, which can all lead to right heart failure.[33]

Indian and Global scenario

As majority types of congenital cardiac defects are nowadays operated in infancy or childhood, incidence of ES is on the decline. The usual life expectancy of ES patients is 20–50 years if the syndrome is diagnosed on time and treated with care; however; some patients might even survive into the sixth decade of their lives.

In India a study was conducted in north-central India that enrolled 34,517 individuals. Out of 34,517 individuals examined, 661 were diagnosed with CHDs, with a prevalence of 19.14 per 1000 individuals. VSD was the most common defect (33%), followed by ASD (19%) and tetralogy of Fallot (16%). 58% diagnosed cases were between 0 and 5 years of age. The prevalence of CHDs in adults was 2.4 per 1000 individuals.[34]

ISSN: 0975-3583,0976-2833 VOL13,ISSUE05,2022

In another study, prevalence of 5.3 per 1000 population was observed. VSD (ventricular septal defect) was the commonest lesion (30.1%), followed by PDA in 21.6 % and ASD in 20.2%. Tetralogy of Fallot was the commonest cyanotic heart disease (8.0%). Maximum numbers of children with heart disease were diagnosed in the age group 6 weeks to 6 years.[35] Other studies with prevalence of CHD are summarised below, where we find a lot of variation (which could be because of population studied and the diagnostic method adopted).

Table 1: Prevalence of CHD in India [(35, 41)]

Sr. No	Author/Year	Total Participants	No. of CHD/1000
1.	Shrestha *et al* 1980	34198	3.2
2.	Gupta *et al* 1992	10264	0.8
3.	Vashishtha*et al* 1993	8449	5.2
4.	Khalil *et al* 1994	10964	3.9
5.	Thakur *et al* 1995	40950	2.25
6.	Chadha *et al* 2001	11833	4.2
7.	Dixit R *et al* 2014	34 517	19.14
8.	Naik S *et al* 2019	39829	5.3
9.	Misra*et al 2009*	118,212	1.3

Analysis of CHD studies done by Yingjuan Liu *et al* concluded that prevalence of CHD is increasing, globally with evidence of severe unmet diagnostic need in Africa. Recent prevalence of CHD in Asia appears to be higher than that in Europe and America. Analysis found heterogeneity among geographical regions, with Africa reporting the lowest prevalence 2.315/1000 and Asia the highest 9.342/1000.[36]

As advanced healthcare is sparsely available in the low- and middle-income countries (LMIC), not many children with CHD reach the adulthood.In North America there is one cardiac center for 120,000 individuals; for Asia this number is whooping 16 million[37].

Around 27,000 patients with CHD underwent cardiac surgery over a one-year period (2016-2017). Of this, about 9,700 patients were infants (<1 year), 1700 neonates (<1 month). If we consider birth prevalence of serious CHD, requiring intervention in the first year of life as 1.6/1000 live births, about 43,000 babies are born in India every year with serious CHD. This means that only about quarter of the cohort needing intervention actually received it[38].

India faces various issues in this regard. Deliveries at home is an obstacle in early diagnosis and intervention, especially for ductus-dependent CHDs. Simple use of pulse oximeter in new-borns before discharge may catch the CHDs. Delays in screening, diagnosis and referral make the situation worse. Again, in India, the sources are not evenly distributed. In Anita Saxena's 'Congenital Heart Disease in India: A Status Report', based on the data received from 47 centers across India, South region was best equipped to intervene more than 70% of the critical CHDs, distantly followed by West (28%), North (17%), East (11.8%), Central (7.6%). North East reported zero operations.

Medical insurance is almost absent in case of CHDs. In a study from Kerala, majority of the families had to suffer financially due to expense of corrective CHD surgeries. Apart from poverty, lack of facilities in the deep pockets or in rural sector is another hurdle and transport of new-borns becomes another matter of concern. There is an additional risk of hypothermia and hypoglycaemia to the new-borns with CHD during their transport[39].

Gender bias also has a role to play here. Report of Ramakrishnan S *et al*. from a tertiary care center in India mentions that girls with CHDs were less likely to get intervention than their male counterpart[40].

ISSN: 0975-3583,0976-2833 VOL13,ISSUE05,2022

Paediatric cardiac care is still evolving in India, where large numbers of CHDs are critical and may lead to death in early life because of lack of awareness and inadequate health facilities.[41]

Conclusion

ES is a multisystem disorder, the roots of which lie in the congenital heart disease. Effective and timely screening may help in effective management of ES. Tailor-made approach in the management of ES is needed considering the heterogeneous nature of the disease. Patient counselling, education and support are important to avail all-round approach. Resource limited setting in LMIC like India has many challenges to overcome. Capacity building in tertiary care centers in India, setting up cardiac and paediatric cardiac units, training the nurses to screen the new-borns, try and increase patient: doctor ratio, especially in rural sector are the key areas to better manage ES in India.

Funding Support and Disclosures regarding Conflict of Interest

No funding was received for writing this article; and there is no conflict of interest to declare.

References

[1]Eisenmenger V. Die angeborenenDefecte der Kammerscheidewand des Herzens. Z Klin Med 1897;32:1-28.

[2] Wood P. The Eisenmenger syndrome or pulmonary hypertension with reversed central shunt.Br Med J 1958; 2: 755–762.

[3] R. Krishna Kumar, Julio Sandoval. Advanced pulmonary vascular disease: the Eisenmenger syndrome.Cardiol Young 2009; 19(E-Suppl. 1): 39–44. doi:10.1017/S1047951109003941

[4]Simonneau G, Galie` N, Rubin LJ, Langleben D, Seeger W, Domenighetti G, Gibbs S, Lebrec D, Speich R, Beghetti M. Clinical classification of pulmonary hypertension. J Am CollCardiol 2004;43(Suppl 1):S5–S12

[5] Diller G-P, Körten M-A, Bauer UMM, et al. Current therapy and outcome of Eisenmenger syndrome: data of the German national register for congenital heart defects. Eur Heart J 2016;37:1449–55

[6]Kempny A, Hjortshøj CS, Gu H, et al. Predictors of death in contemporary adult patients with Eisenmenger syndrome: a multicenter study. Circulation 2017;135:1432–40

[7]Kempny A, Dimopoulos K, Gatzoulis MA. Declining incidence and prevalence of Eisenmenger syndrome in the developed world: a triumph of modern medicine. Heart. 2017;103:1313– 1314.

[8] Heath D, Edwards JE. The pathology of hypertensive pulmonary vascular disease; a description of six grades of structural changes in the pulmonary arteries with special reference to congenital cardiac septal defects.Circulation.1958; 18: 533-547.1958/10/01.

[9]Kempny A, Dimopoulos K, Uebing A, et al. Reference values for exercise limitations among adults with congenital heart disease. Relation to activities of daily life--single centre experience and review of published data. Eur Heart J 2012;33:1386–96.

[10]Arvanitaki A, Mouratoglou SA, Evangeliou A, et al. Quality of life is related to haemodynamics in precapillary pulmonary hypertension. Heart Lung Circ 2020;29:142–8.

[11]Dimopoulos K, Diller GP, Koltsida E, et al. Prevalence, predictors, and prognostic value of renal dysfunction in adults with congenital heart disease. Circulation. 2008;117:2320–2328.

[12]Baskar S, Horne P, Fitzsimmons S, et al. Arrhythmia burden and related outcomes in Eisenmenger syndrome. Congenit Heart Dis 2017;12:512–9.

ISSN: 0975-3583,0976-2833 VOL13,ISSUE05,2022

[13] Van De BruaeneA, Delcroix M, Pasquet A, et al. Iron deficiency is associated with adverse outcome in Eisenmenger patients. Eur Heart J 2011;32:2790–9.

[14]Galiè N, Humbert M, Vachiery J-L, et al. 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension: the joint Task force for the diagnosis and treatment of pulmonary hypertension of the European Society of cardiology (ESC) and the European respiratory Society (ERS): endorsed by: association for European paediatric and congenital cardiology (AEPC), International Society for heart and lung transplantation (ISHLT). EurRespir J 2015;46:903–75.

[15]Hjortshøj CMS, Kempny A, Jensen AS, et al. Past and current cause-specific mortality in Eisenmenger syndrome.Eur Heart J 2017;38:2060–7

[16]Saha A, Balakrishnan KG, Jaiswal PK, Venkitachalam CG, Tharakan J, Titus T, et al. Prognosis for patients with Eisenmenger syndrome of various aetiology. Int J Cardiol 1994;45:199-207

[17]Moons P, Luyckx K, Thomet C, et al. Physical functioning, mental health, and quality of life in different congenital heart defects: comparative analysis in 3538 patients from 15 countries. Can J Cardiol. 2021;37:215–223.

[18] Alexandra Arvanitaki , George Giannakoulas, Helmut Baumgartner, et al. Eisenmenger syndrome: diagnosis, prognosis and clinical management. Heart 2020;0:1–8. doi:10.1136/ heartjnl-2020-316665

[19]Galiè N, Humbert M, Vachiery J-L, et al. 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension: the joint Task force for the diagnosis and treatment of pulmonary hypertension of the European Society of cardiology (ESC) and the European respiratory Society (ERS): endorsed by: association for European paediatric and congenital cardiology (AEPC), International Society for heart and lung transplantation (ISHLT). EurRespir J 2015;46:903–75.

[20] Alexandra Arvanitaki, Michael A. Gatzoulis, Alexander R. Opotowsky*et al*. Eisenmenger Syndrome, JACC State-of-the-Art Review; VOL. 79, NO. 12, 2022 https://doi.org/10.1016/j.jacc.2022.01.022

[21]Humbert M, Morrell NW, Archer SL, et al. Cellular and molecular pathobiology of pulmonary arterial hypertension. J Am CollCardiol. 2004;43(suppl 1):13S–24S.

[22]Apostolopoulou SC, Manginas A, Cokkinos DV, Rammos S. Effect of the oral endothelin antagonist bosentan on the clinical, exercise, and haemodynamic status of patients with pulmonary arterial hypertension related to congenital heart disease. Heart. 2005;91:1447–1452.

[23] Diller G-P, Körten M-A, Bauer UMM, et al. Current therapy and outcome of Eisenmenger syndrome: data of the German national register for congenital heart defects. Eur Heart J 2016;37:1449–55.

[24]Guarguagli S, Kempny A, CazzoliI, et al. Efficacy of catheter ablation for atrial fibrillation in patients with congenital heart disease. Europace 2019;21:1334–44.

[25]Giannakoulas G, Boutsikou M. The Gordian knot of thromboembolism in congenital heart disease. Heart 2015;101:1523–4.

[26] Baumgartner H, De Backer J, BabuNarayan SV, et al. 2020 ESC guidelines for the management of adult congenital heart disease. Eur Heart J. 2021;42(6):563–645. https://doi.org/ 10.1093/eurheartj/ehaa554

[27]Knight M, Kurinczuk JJ, Spark P, Brocklehurst P. United Kingdom Obstetric Surveillance System (UKOSS) Annual Report 2007. Oxford: National Perinatal Epidemiology Unit; 2007

[28]Weiss BM, Zemp L, Seifert B, Hess OM. Outcome of pulmonary vascular disease in pregnancy: a systematic overview from 1978 through 1996. J Am CollCardiol 1998;31:1650–7.

ISSN: 0975-3583,0976-2833 VOL13,ISSUE05,2022

[29]Katsuragi S, Yamanaka K, Neki R, Kamiya C, Sasaki Y, Osato K, et al. Maternal outcome in pregnancy complicated with pulmonary arterial hypertension.Circ J 2012;76:2249–54.

[30]Galiè N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. EurRespir J 2015; 46: 903–975

[31]Hemnes AR, Kiely DG, Cockrill BA, et al. Statement on pregnancy in pulmonary hypertension from the Pulmonary Vascular Research Institute. PulmCirc 2015; 5: 435–465

[32]Hsu CH, Gomberg-Maitland M, Glassner C, et al.The management of pregnancy and pregnancy-related medical conditions in pulmonary arterial hypertension patients.Int J ClinPractSuppl 2011; 175: 6–14.

[33]Jais X, Olsson KM, Barbera JA, et al. Pregnancy outcomes in pulmonary arterial hypertension in the modern management era. EurRespir J 2012; 40: 881–885

[34]Dixit R, Rai SK, Yadav AK, Lakhotia S, Agrawal D, Kumar A, Mohapatra B. Epidemiology of Congenital Heart Disease in India. Congenit Heart Dis. 2015 Sep-Oct;10(5):437-46. doi: 10.1111/chd.12220. Epub 2014 Sep 8. Erratum in: Congenit Heart Dis. 2019 Nov;14(6):1214. PMID: 25196372.

[35]Naik S et al. Int J ContempPediatr. 2019 Mar;6(2):275-279

[36]Liu Y, Chen S, Zühlke L, Black GC, Choy MK, Li N, Keavney BD. Global birth prevalence of congenital heart defects 1970-2017: updated systematic review and meta-analysis of 260 studies. Int J Epidemiol. 2019 Apr 1;48(2):455-463. doi: 10.1093/ije/dyz009. PMID: 30783674; PMCID: PMC6469300.

[37]Pezzella T. Worldwide maldistribution of access to cardiac surgery. J ThoracCardiovasc Surg. 2002;123:1016-17.

[38] Kumar RK, Shrivastava S. Pediatric heart care in India. Heart. 2008;94:984-90.

[39] Raj M, Paul M, Sudhakar A, Varghese AA, Haridas AC, Kabali C, et al. Micro-economic impact of congenital heart surgery: Results of a prospective study from a limitedresource setting. PLoS One. 2015;10:e0131348

[40]Ramakrishnan S, Khera R, Jain S, Saxena A, Kailash S, Karthikeyan G, et al. Gender differences in the utilisation of surgery for congenital heart disease in India. Heart.2011; 97:1920-5.

[41] Anita Saxena, Congenital Heart Diseases in India: A status report, Indian Journal of Paediatrics , Volume 72 – July 2005