INTRODUCTION

Anemia is an important risk factor for morbidity and mortality in patients with congenital cyanotic heart disease (CCHD) ***(Paul and Paul, 2004).***

Iron deficiency (ID) is one of the most common nutritional deficiencies worldwide and is the leading cause of anemia, especially in children. The main function of iron in the human body is to carry oxygen to the tissues from the lungs in the form of hemoglobin (Hb) ***(Felker et al., 2006; Andron et al., 2003).***

ID represents a spectrum ranging from iron depletion to iron deficiency anemia (IDA). In infants, ID and IDA result in developmental delays, behavioral disturbances, and irreversible impairment of child's learning ability. IDA can be cured, but altered cognitive performance may not be correctable. Clinical interest of infant ID focuses on early recognition of subclinical ID to prevent the systemic complications of IDA ***(Broberg et al., 2006).***

Diagnosis of ID can be established by different hematological and biochemical In CCHD with a right to left shunt, arterial oxygen saturation decreases and red blood cell count may reach to high level and hyper viscosity develops. In addition, in anemic patients especially those with microcytic iron deficiency anemia, permeability of microcytic erythrocytes

decreases in comparison to normocytic cells, therefore thromboembolic and cardiovascular events are encountered more commonly ***(Brugnara, 2003).***

The patients with heart disease are frequently anemic and anemia has a high prevalence among them in the absence of vitamin or mineral deficiency, hemolytic or other definable causes. However, it was emphasized that more than one third of the patients with CCHD had iron deficiency anemia, which may have been aggravated by concomitant disorders or a combination of factors ***(Looker et al., 1997).***

Studies were clear that preoperative anemia especially in heart diseases gives rise to postoperative cardiac events, complications and death ***(Lone et al., 2006).***

Transferrin saturation and serum ferritin measurements have been noted to be insensitive and inaccurate measures to detect functional iron deficiency. Recently, the reticulocyte hemoglobin content (RET-He) has been shown to be a sensitive and specific indicator of functional iron deficiency ***(Roodpeyma et al., 2002).***

AIM OF THE WORK

To evaluate the role of reticulocyte hemoglobin content in detection of functional anemia in patients with congenital cyanotic heart disease.

CONGENITAL CYANOTIC HEART DISEASE

Definition:-

Congenital heart disease (CHD) can be defined as an anatomic malformation of the heart or large vessels which occurs during intrauterine development, irrespective of the age at presentation ***(Patra et al., 2015).***

Epidemiology:-

It is the most common congenital problem in children representing nearly 25% of all congenital malformations. Congenital heart diseases (CHDs) account for 6-10 % of all the infant deaths, and 20 - 40 % of all infant deaths from malformations ***(Muhll, 2012).***

The incidence of CHD in different studies varies from about 4/1000 to 50/1000 live birth. Variation is primarily due to the use of different methods to detect CHD (i.e., fetal echocardiography versus postnatal referral to a cardiac center) ***(Hoffman et al., 2002)***.

Congenital cyanotic heart disease (CCHD) accounts for 25% of all cases of CHD ***(Patra et al., 2015).***

The most common congenital heart defect is a bicuspid aortic valve (BAV), with a prevalence estimated between 0.5 and 2 percent, but as an isolated lesion it is rarely diagnosed in infancy ***(Nikyar et al., 2011).***

The next most common defects are ventricular septal defects (VSDs) and secundum atrial septal defects (ASDs, prevalence of 4 and 2 per 1000 live births, respectively. Tetralogy of Fallot (TOF) is the most common cyanotic CHD (0.5 per 1000 births) ***(Gupta-Malhotra et al., 2008).***

Critical CHD accounts for approximately 25 percent of all CHD. In infants with critical CHD, the risk of morbidity and mortality increases when there is a delay in diagnosis and timely referral to a tertiary center ***(Thienpont et al., 2007).***

Table (1): Relative frequency of major congenital heart lesion ***(Nelson, 2016).***

Lesion	% of all lesion
Ventricular septal defect	35-30
Atrial septal defect (secundum)	6-8
Patent dectus arteriosus	6-8
Coarctation of aorta	5-7
Tetralogy of fallot	5-7
Pulmonary valve stenosis	5-7
Aortic valve stenosis	4-7
D-Trasnposition of great arteries	3-5
Hypoplastic left ventricle	1-3
Hypoplastic right ventricle	1-3
Trauncus arteriosus	1-2
Total anomalous pulmonary venous return	1-2
Tricuspid atresia	1-2
Single ventricle	1-2
Double-outlet right ventricle	1-2
Others	5-10

*Excluding patent ductus arteriousus in preterm neonates, bicuspid aortic valve physiologic peripheral pulmonic stenosis, and mitral valve prolapse.

Etiology:-

The cause of most congenital heart defects is still unknown.

Etiology of most cases of CHD is thought to be multifactorial representing 90% of the cases, 8% of the cases due to RET-He omosomal/genetic factors, and 2% of the cases due to environmental teratogens ***(Tanner et al., 2005).***

The majority of genetic causes of CHD are sporadic genetic changes or RET-He omosomal abnormalities. The most common RET-He omosomal abnormalities associated with a heart defect are Down syndrome; trisomies 13 and 18; Turner syndrome; 16 22q11 deletion syndromes, including DiGeorge deletion; and Williams, Alagille, and Noonan syndromes ***(Bishara and Clericuzio, 2010).***

Environmental factors for the development of CHD include maternal disease, drug exposure and viral infections. Many teratogens have been identified in the past 20 years, with thalidomide being one of the most well-known.

Anticonvulsants have been shown to cause coarctation of the aorta, pulmonary stenosis, and PDA. Phenytoin and valproic acid are known to cause coarctation of the aorta, VSD, TGV, TOF, pulmonary atresia, aortic stenosis, and pulmonic stenosis ***(Lindhout et al., 2002).***

Lithium is associated with Ebstein anomaly, ASD, and tricuspid atresia. Alcohol is known to cause VSD, ASD, coarctation of the aorta, and TOF.

A recent study found that use of angiotensin-converting enzyme inhibitor during the first trimester was associated with a 2.9% incidence of a major congenital malformation, including ASD, VSD, and pulmonic stenosis ***(Cooper et al., 2006).***

Compared to pregnant women without diabetes, insulin-dependent diabetic women with poor glucose control have five times greater risk of bearing a child with cardiac anomalies, including cardiomyopathy, VSD, double-outlet right ventricle, TGV, truncus arterosus, and coarctation of the aorta ***(Abu-Sulaiman et al., 2007).***

Recently, maternal obesity has been linked to CHD. Rubella is the only viral illness associated with an increase in congenital cardiac defects, such as PDA, pulmonary stenosis, VSD, and ASD ***(Nakai et al., 2008).***

Positive family history is considered one of the most common risk factors for CHD Recurrence risk increases by three- to fourfold when a parent or sibling has CHD and increases by 10-fold if two first-order relatives have CHD ***(Groot et al., 2008).***

Classification:-

Several classifications of CHD have been introduced.

Congenital heart defects may be classified into **Acyanotic** and **Cyanotic** depending upon whether the patients clinically exhibit cyanosis.

Acyanotic heart lesions can be classified according to the predominant physiologic load that they place on the heart. The cyanotic heart lesions may be further classified according to the increase or decrease of the Pulmonary Blood Flow ***(Bradshaw et al., 2012).***

CHD may also be classified into:-

- **Ductal-Independent Lesions:** The pulmonary blood flow or the systemic blood flow does not depend on the shunting of the blood via the PDA.
- **Ductal-dependent lesions:** PDA is required to shunt blood to the pulmonary artery or to the descending aorta and thus, to the systemic circulation.

The lesions that are dependent upon the PDA to provide pulmonary blood flow include: - (tricuspid atresia with significant pulmonary stenosis, pulmonary atresia with intact ventricular septum, tetralogy of Fallot with significant pulmonary stenosis or atresia, and Epstein's anomaly with significant pulmonary stenosis).

The lesions that are dependent upon the PDA to provide systemic blood flow include: - Hypo plastic left heart syndrome, critical aortic stenosis, interrupted aortic arch, and significant coarctation of the aorta ***(Jones et al., 2006).***

A pathophysiological classification, namely, a classification based upon the clinical consequences of structural defects impairing the physiology of blood circulation, seems more reasonable:

- CHD with increased pulmonary blood flow (septal defects without pulmonary obstruction and left-to right shunt).
- CHD with decreased pulmonary flow (septal defects with pulmonary obstruction and right-to-left shunt).
- CHD with obstruction to blood progression and no septal defects (no shunt).
- CHD so severe as to be incompatible with postnatal blood circulation :- Very severe forms of CHD, such as complete transposition of the great arteries, total anomalous pulmonary venous drainage, aortic or pulmonary atresia, and interruption/ atresia of the aortic arch, are perfectly compatible with fetal circulation and full-term pregnancy
- CHD silent until adult age: - Congenitally corrected transposition of the great arteries, Wolff–Parkinson–White syndrome, Congenital anomalies of coronary arteries, Bicuspid Aortic Valve (BAV) ***(Praagh et al., 2002).***

Table (2): Classification of congenital heart defects ***(Bradshaw et al., 2012).***

Acyanotic CHD	Cyanotic CHD
▪ **Lesions Resulting in Increased Volume Load** ○ **Left-To-Right Shunt** • Ventricular Septal Defect (VSD) • Atrial Septal Defect (ASD) • Patent Ductus Arteriosus (PDA) • Atrio-ventricular Septal Defect (AVSD) ○ **Regurgitant lesions** • Pulmonary Valvular Insufficiency And Congenital Absence Of The Pulmonary Valve • Congenital Mitral Insufficiency • Mitral Valve Prolapse • Tricuspid Regurgitation ▪ **Lesions Resulting in Increased Pressure Load** ○ **Obstructive Lesions** • Pulmonary Stenosis (PS) • Aortic Stenosis (AS) • Coarctation of the Aorta	▪ **Cyanotic Lesions with Decrease In Pulmonary Blood Flow** • Tetralogy Of Fallot • Tetralogy Of Fallot With Pulmonary Atresia • Tricuspid Atresia • Double Outlet Right Ventricle • Transposition Of Great Arteries With VSD And PS • Ebstein Anomaly Of The Tricuspid Valve ▪ **Cyanotic Lesions with Increase In Pulmonary Blood flow** • D-transposition of the great arteries • D-Transposition Of The Great Arteries With Intact Ventricular Septum • Transposition Of The Great Arteries With VSD • DORV With PS • Total Anomalous Pulmonary Venous Connection • Single Ventricle • Truncus Arteriosus • Hypoblastic Left Heart Syndrome

Pathophysiology

Understanding the fetal circulation and the circulatory shunts can form a framework for approaching congenital heart diseases.

Fetal Circulation

Fetal circulation differs from adult circulation in several ways. Almost all differences are attributable to the fundamental difference in the site of gas exchange. In the adult, gas exchange occurs in the lungs. In the fetus, the placenta provides the exchange of gases and nutrients.

Course of fetal circulation

There are four shunts in fetal circulation: placenta, ductus venosus, foramen ovale, and ductus arteriosus.

- The placenta receives the largest amount of combined (i.e., right and left) ventricular output (55%) and has the lowest vascular resistance in the fetus.

- The superior vena cava (SVC) drains the upper part of the body, including the brain (15% of combined ventricular output), whereas the inferior vena cava (IVC) drains the lower part of the body and the placenta (70% of combined ventricular output). Because the blood is oxygenated in the placenta, the oxygen saturation in the IVC (70%) is higher than that in the SVC (40%). The highest PO_2 is found in the umbilical vein (32 mm Hg).

- Most of the SVC blood goes to the right ventricle (RV). About one third of the IVC blood with higher oxygen saturation is directed by the crista dividens to the left atrium (LA) through the foramen ovale, whereas the remaining two thirds enters the RV and pulmonary artery (PA). The result is that the brain and coronary circulation receive blood with higher oxygen saturation (PO_2 of 28 mm Hg) than the lower half of the body (PO_2 of 24 mm Hg)

- Less oxygenated blood in the PA flows through the widely open ductus arteriosus to the descending aorta and then to the placenta for oxygenation.

(Park, 2016)

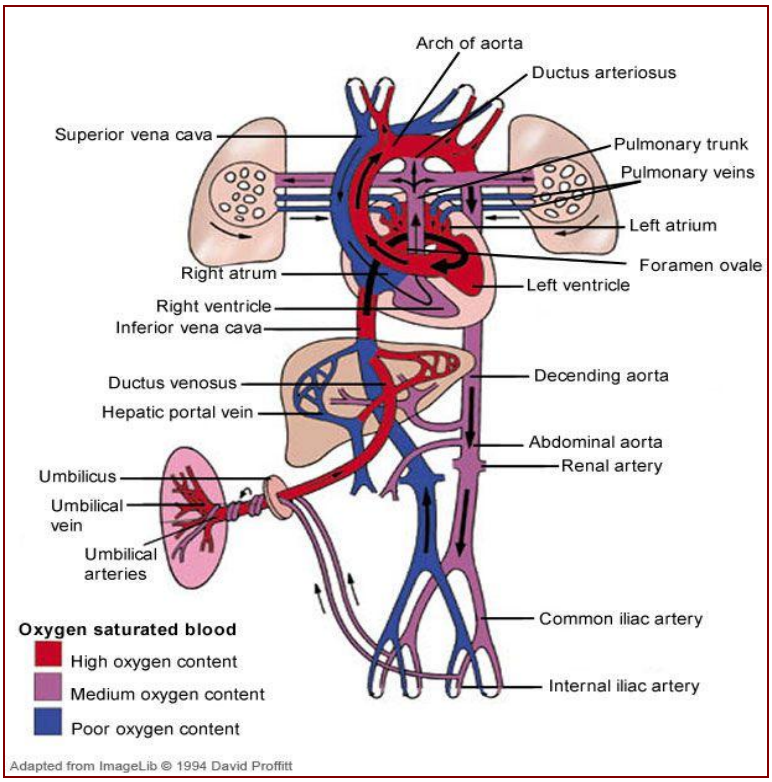

Figure (1): Diagram of the fetal circulation showing the four sites of shunt: placenta, ductus venosus, foramen ovale, and ductus arteriosus ***(Guntheroth et al., 2008).***

Changes in Circulation after Birth

The primary change in circulation after birth is a shift of blood flow for gas exchange from the placenta to the lungs. The placental circulation disappears, and the pulmonary circulation is established.

1. Interruption of the umbilical cord results in the following:

    a. An increase in systemic vascular resistance as a result of the removal of the very-low-resistance placenta

b. Closure of the ductus venosus as a result of lack of blood return from the placenta

2. Lung expansion results in the following:

a. A reduction of the pulmonary vascular resistance (PVR), an increase in pulmonary blood flow, and a fall in PA pressure.

b. Functional closure of the foramen ovale occurs as a result of increased pressure in the LA in excess of the pressure in the right atrium (RA).

The LA pressure increases as a result of the increased pulmonary venous return to the LA, and the RA pressure falls as a result of closure of the ductus venosus.

c. Closure of patent ductus arteriosus (PDA) as a result of increased arterial oxygen saturation

(Park, 2016)

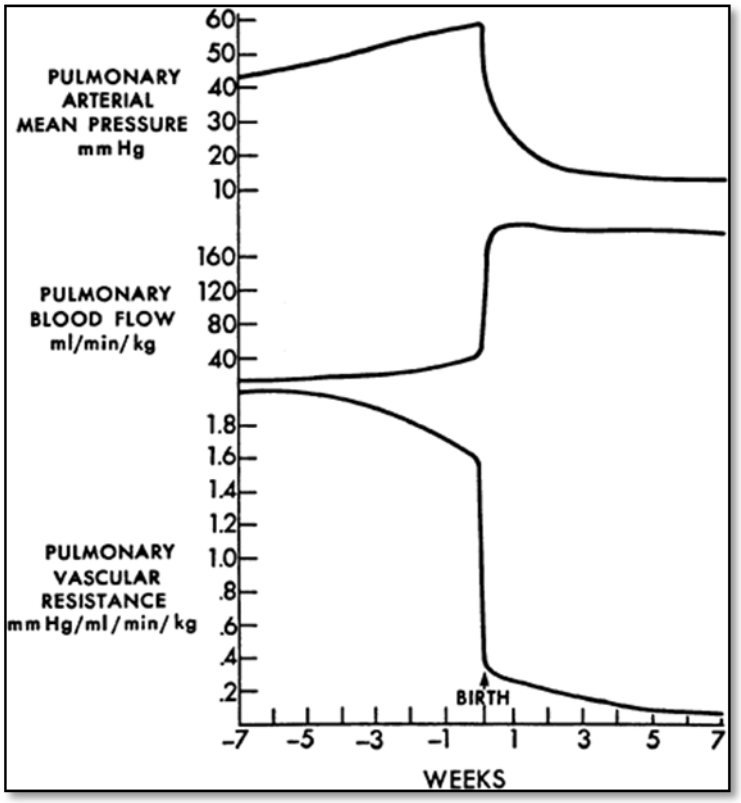

Figure (2): Changes in pulmonary artery pressure, pulmonary blood flow, and pulmonary vascular resistance, during the 7 weeks preceding birth, at birth, and in the 7 weeks after birth. The prenatal data were derived from lambs and the postnatal data from other species ***(Rudolph, 1974).***

Pathophysiology:-

Congenital cyanotic heart diseases will necessarily cause many pathophysiologic changes; many of this changes are compensatory mechanisms occur in patients with CCHD. These are beneficial to the patients but when overcompensation occurs, complications tend to dominate the clinical picture.