INTRODUCTION

PPHN is a syndrome characterized by systemic arterial hypoxemia, secondary to elevated pulmonary vascular resistance with resultant shunting of pulmonary blood flow through foramen ovale and/or ductus arteriosus to the systemic circulation***(Chandran et al., 2004).***

Pulmonary hypertension of the newborn (PHN) occurs in 1.9 per 1000 live births, but a wide variation in the incidence 0.43–6.82 per 1000 live births has been reported between countries ***(Anne and Babita, 2005).***

The pathophysiologies underlying PPHN are under-development (pulmonary hypoplasia, congenital diaphragmatic hernia), maldevelopment (chronic hypoxia, placental insufficiency, elevated pulmonary pressure), or maladaptation (triggered by acidosis hypoxemia and hypercarbia) of pulmonary vasculature- PPHN is associated with meconium aspiration syndrome (50%), pneumonia/ sepsis (20%), idiopathic (20%) RDS (5%) and other causes (5%) such as/ asphyxia, congenital diaphragmatic hernia, alveolarcapillary dysplasia and polycythemia***(Meera et al., 2011).***

The gold standard is an echocardiogram to differentiate between PPHN and a cyanotic congenital heart defect as well as to determine pulmonary arterial pressures and direction of shunting across the ductus arteriosus***(National Health Service, 2007).***

Persistent pulmonary hypertension of the newborn is a medical emergency in which immediate management is essential and is directed towards reversing hypoxemia, improving pulmonary perfusion by reducing pulmonary vascular resistant, increasing systemic pressures to reverse the right-to-left intracardiac shunting and minimizing hypoxic-ischemic end-organ injury.

Management includes the following:

- Preventing and anticipating PPHN.
- Ventilatory support to achieve optimal oxygenation.
- Hemodynamic support to maintain adequate cardiac output and optimal systemic blood pressure.
- Reducing the raised PVR.

Response to therapy is often unpredictable, transient, and complicated by the adverse effects of drugs or mechanical ventilation as well as other associated metabolic and physiologic derangements that are known to occur in infants with PPHN ***(Brig et al., 2011).***

Inhaled nitric oxide (iNO) is a selective pulmonary vasodilator and widely accepted as the gold standard treatment in PPHN, Its usage has contributed to reduced rates of extracorporeal membrane oxygenation (ECMO).Nevertheless 30% of patients with PPHN are iNO non responders, and

alternative treatment options are required. Milrinone, a selective inhibitor of phosphodiesterase (PDE) III in cardiac myocytes and vascular smooth muscle has been shown to reduce PVR and pulmonary artery pressure ***(Patrick et al., 2006).***

Magnesium Sulphate is vasodilatory agents like tolazoline and prostacyclin, inhaled nitric oxide (NO), and extra-corporeal membrane oxygenation (ECMO). And used as options in treatment of PPHN ***(*Chandran *et al., 2004).***

AIM OF THE WORK

Comparison between effectiveness of milrinone versus magnesium sulphate in neonatal pulmonary hypertention in multicenter NICU.

NORMAL PULMONARY VASCULAR DEVELOPMENT

The pulmonary circulation is a highly specialized vascular bed that physically and functionally connects the heart and the lungs. The interdependence of these two organs is illustrated in embryonic development, when the lung endoderm protrudes into the surrounding mesoderm as the heart tube elongates and folds into structurally distinct chambers. The pulmonary vascular precursors then undergo highly stereotyped cellular maturation and patterning to form a multilayered vascular network that parallels the airways and links the arterial and venous poles of the heart. Upon the first breath, the mature pulmonary circulation is poised to receive the entire cardiac output for efficient gas exchange, and deliver oxygenated blood to the systemic circulation. Prior studies into the role of angiogenesis and vasculogenesis in pulmonary vascular development have not clearly yielded the identity of pulmonary vascular precursors, or the signals coordinating vascular maturation ***(Peng et al., 2013).***

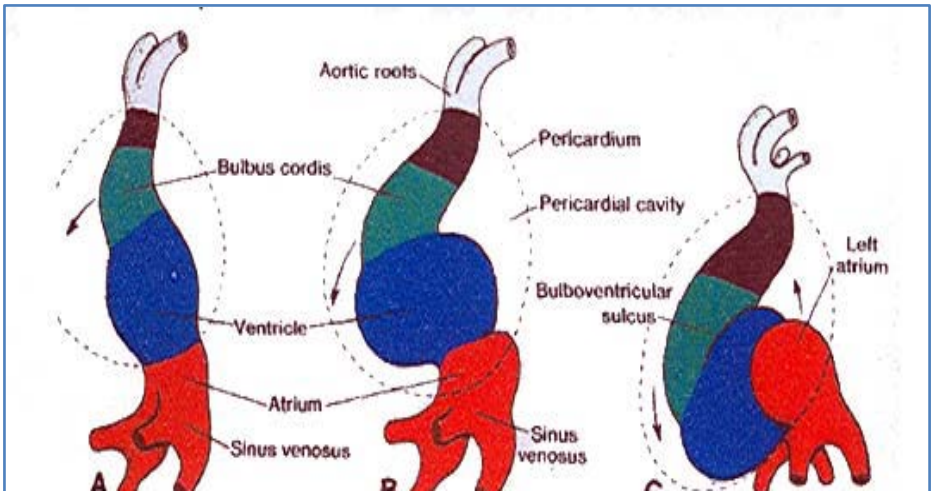

Fig. (1): Formation of cardiac loop.

A: 22 days, B; 23 day, C: 24 day

Broken Line:pericardium *(Sadler, 2004).*

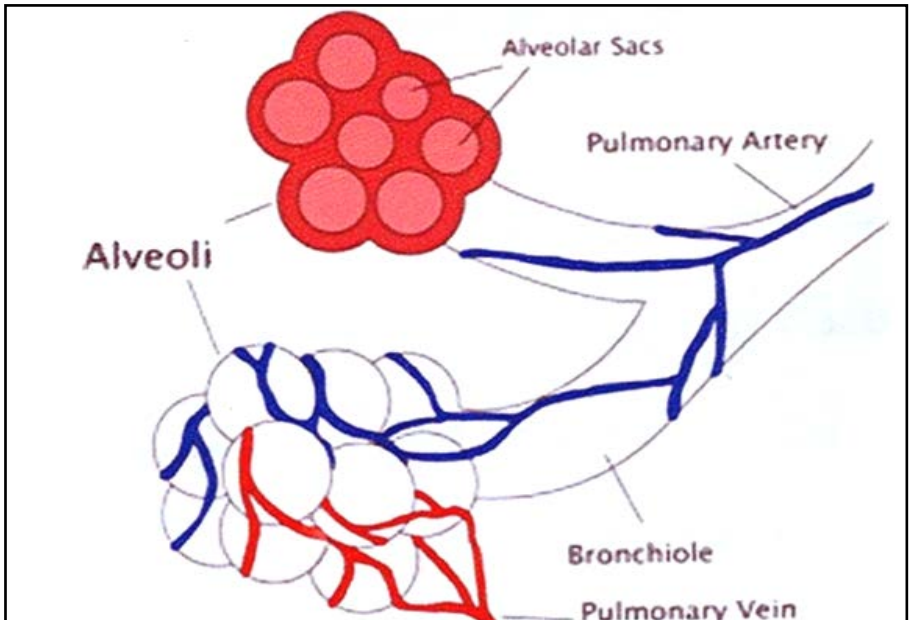

Fig. (2): Diagram of the alveoli with both cross-section and external view ***(Richard, 2005).***

The lung primordia are present by twenty eight days of gestation as an endothelial pair of lung bud from the esophagus. Three lung buds can be discerned on the right and two on the left by the fifth week of gestation. The vascular supply to the lung buds initially comprises of paired segmental arteries arising from the dorsal aorta.These arteries normally involuteArterial connections may persist in origin of one pulmonary artery from the aorta, historically known as hemitruncus**(Pool et al.,1962).**

By one month of age, the paired sixth aortic arches give off branches to the developing lung. The left sixth aortic arch gives rise to the main pulmonary artery and the proximal part of the left hilar branches. The connection of the left sixth arch with the aorta persists during fetal life as the ductus arteriosus.The right sixth aortic arch provides the proximal part to the right pulmonary artery **(Risan et al., 1988).**

Besides the different origins of the pulmonary artery segments, two other processes probably contribute to the development of the lung vasculature:angiogenesis and vasculogensis**(Morin etal.,1995).**

All bronchial generations and its accompanying preaccinar arteries are present by the sixteenth week of gestation. During the next five month of fetal life additional intra acinar respiratory units are added with accompanying arteries. The preacinar arteries and those at terminal bronchiolus level are muscular and thick walled but the intra acinar vessels are largely non muscular **(Hilsop et al., 1972).**

Later in gestation during the third trimester, there is a dramatic increase in development of the more distal lung, as alveolar ducts and saccules develop Normally, at this point in gestation, the pulmonary arteries associated with the alveolar duct lack muscularization**(Reid etal.,1986)**

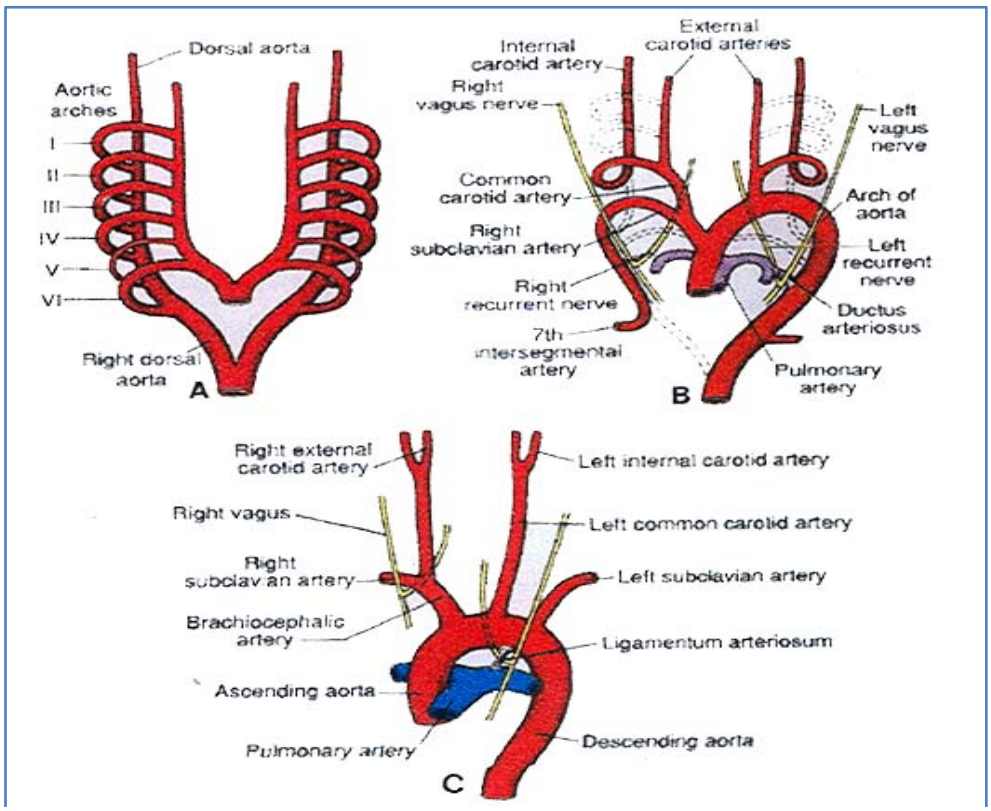

Fig. (3):A. Aortic arches and dorsal aortae before transformation into the definitive vascular pattern. B. Aortic arches and dorsal aortae after the transformation.Broken lines, obliterated components. Note the patent ductus arteriosus and position of the seventh intersegmental artery on the left C.The great arteries in the adult. Compare the distance between the place of origin of the left common carotid artery and the left subclavian in B and C. After disappearance of the distal part of the sixth aortic arch (the fifth arches never form completely), the right recurrent laryngeal nerve hooks around the right subclavian artery. On the left the nerve remains in place and hooks around the ligamentum arteriosum ***(Sadler, 2004).***

Lung blood vessels: normal structure and function of the pulmonary and bronchial circulations:

The vascular system of the lung is divided into the pulmonary and bronchial systems.

The pulmonary arteries supply the intrapulmonary structures and ultimately regulate gas exchange; vessels branch with the airways but branch into an extensive capillary network only at the level of respiratory bronchioles and alveoli.

The bronchial system is the nutrient supply to the lung and perfuses the capillary bed within the bronchial wall.***(Shaw et al., 2000).***The pulmonary artery accompanies the airways but gives off many more branches than the airway. ***(DeMello et al., 2002)***

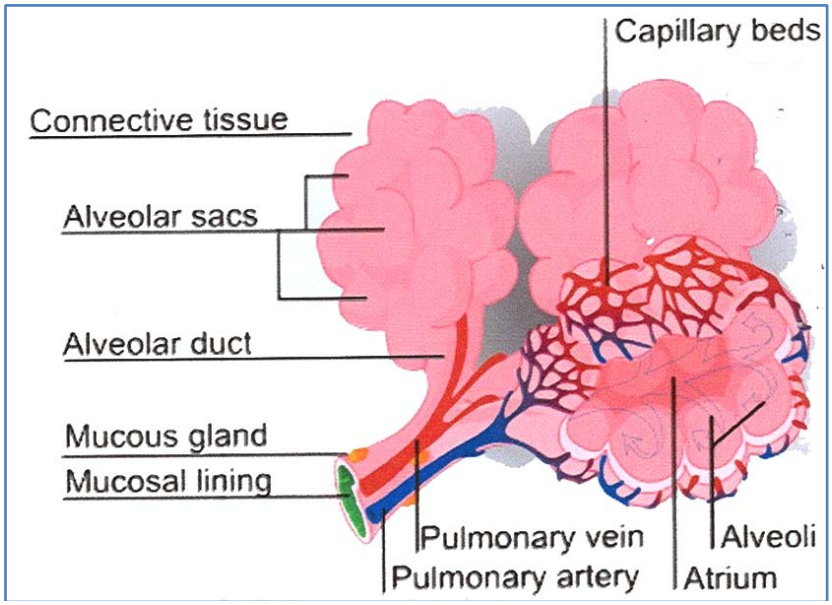

Fig. (4): Vascular supply to the lung ***(Daniel et al., 2003).***

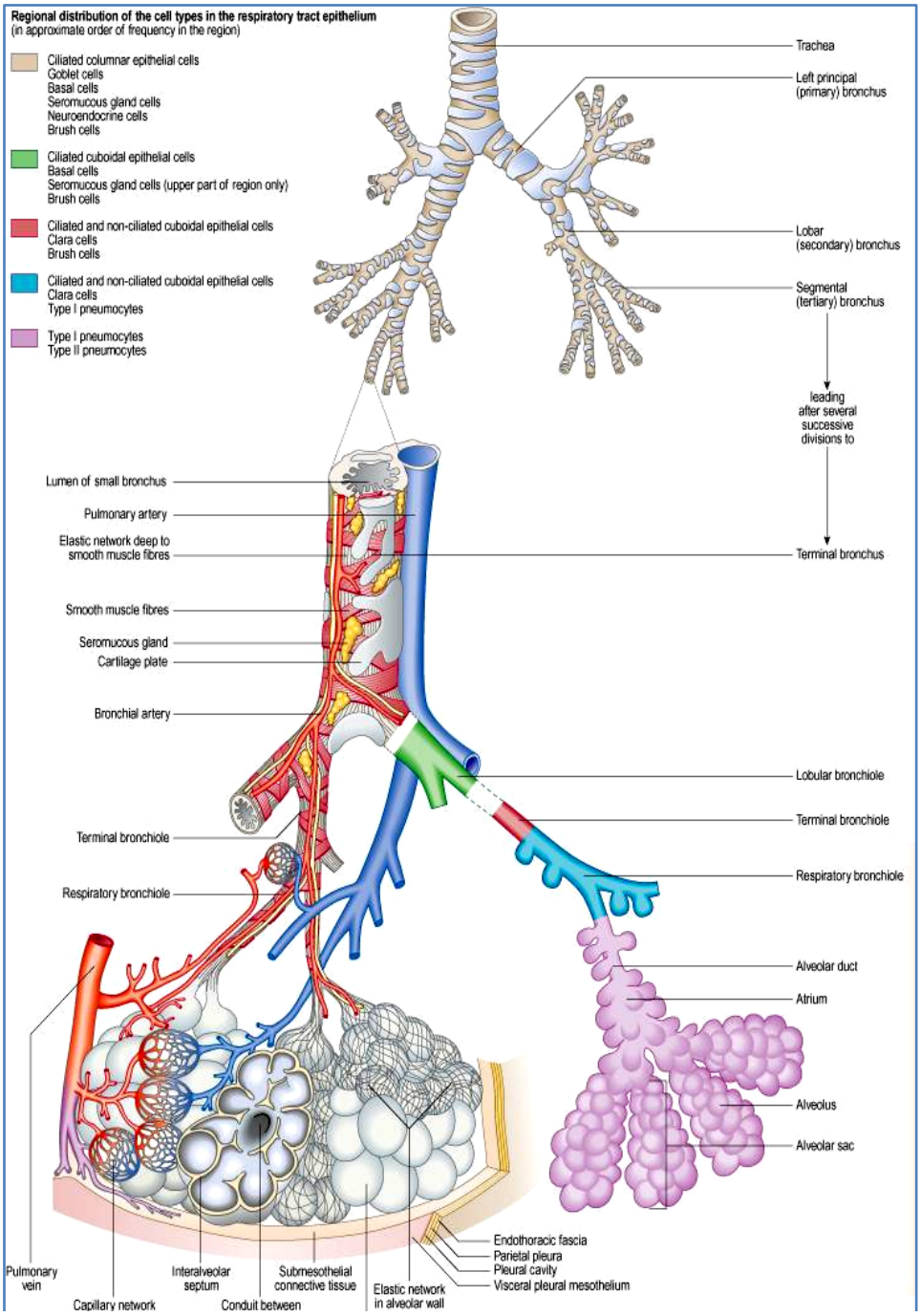

Fig. (5): Anatomy of tracheobronchial tree (www.graysanatomyonline.com).

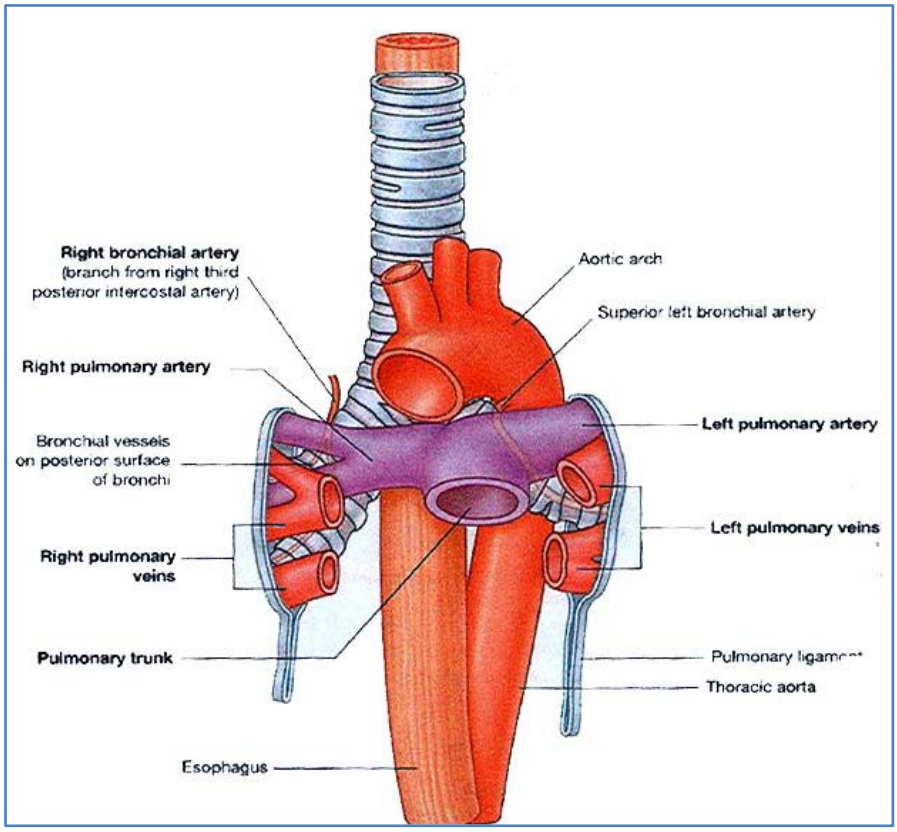

Fig. (6): Pulmonary artery and vein***(Richard, 2005).***

The Wall Structure of the Pulmonary Artery Tree

As in the systemic circulation, the wall structure of pulmonary arteries and their smooth muscular content differ according to their location in pulmonary vascular tree. For any given caliber, however, the medial smooth muscle layer of pulmonary arteries is thinner than that of the systemic vasculature, reflecting the lower pressure seen by the normal pulmonary circulation. The larger elastic pulmonary arteries (> 1000 um in diameter) are found in central pulmonary arteries and extra lobular pulmonary arteries, these arteries have an adventitial, muscular and intimal layer, the muscular layer is bounded by internal and external elastic lamina and accounts for 1-2 percent of the external diameter. The muscular arteries (100 to 1000 um in diameter) track bronchioles with lobules are smaller in size and lack an internal elastic lamina, have a thick muscular layer that is 2-5 percent of external diameter. More distal in pulmonary artery tree are pulmonary arterial (< 100 um in diameter) which is partially muscularized arteries with an incomplete muscular layer. Finally, the non-muscular artery (> 15 um in diameter) is similar to alveolar capillaries and the smooth muscular layer is replaced by pericytes, it has been suggested that pericytes may produce and organize the surrounding matrix and basement membrane. In addition pericytes may differentiate into smooth muscle cell and constitute the site vascular remolding in pulmonary hypertension ***(Weibel, 1999).***

The lung can triple its volume when expanding from function residual capacity to total lung capacity. This change in lung volume has opposing effects on the alveolar vessels (capillaries) and extra alveolar vessels (arteries and vein). As the lung expands**,** the diameter of the extra – alveolar vessels increases secondary to the radial traction created by the expanding alveoli in contrast**,** the diameter of alveolar capillaries decreases as lung expands and alveolar setae lengthen. The exception to the later are the alveolar vessels termed " Corner vessels" The corner vessels differ from the other alveolar capillaries in their ability to resist the effect of high alveolar pressure that causes the closure of most alveolar sepal capillaries **(*Gil and Ciurea, 1996)*.**

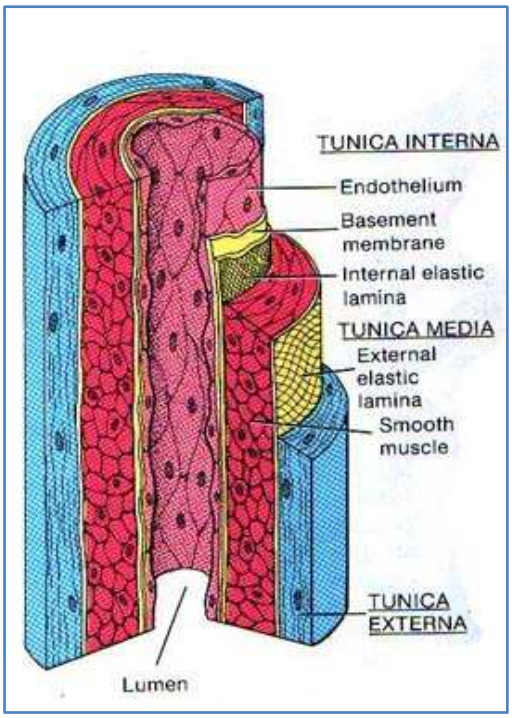

Fig. (7): The Wall Structure of the Pulmonary artery
www.mananatomy.com

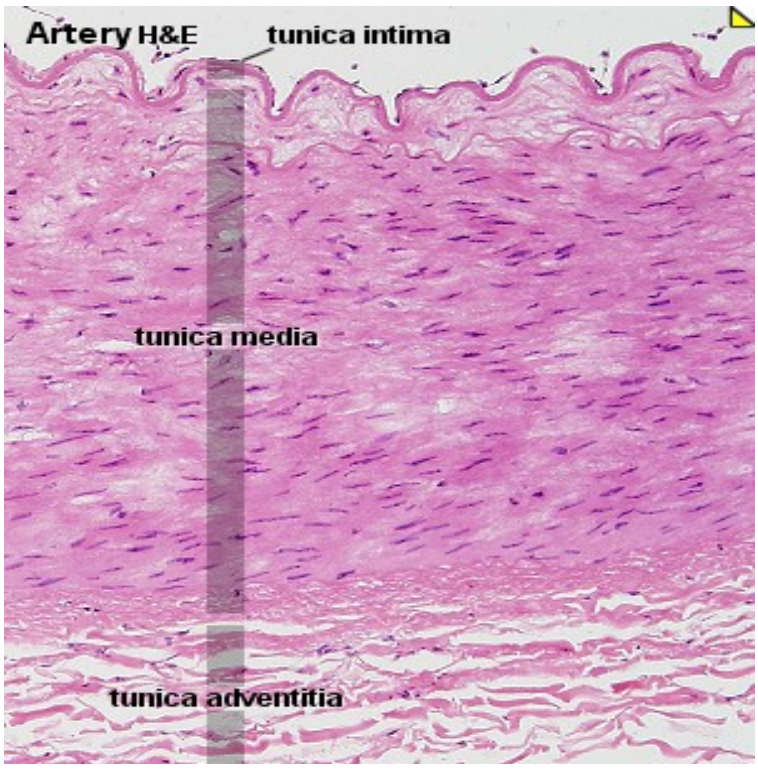

Fig. (8): Blue Histology - Vascular System
www.lab.anhb.uwa.edu.au.

Fetal Circulation

During pregnancy, the fetal circulation system works differently than after birth. The fetus is connected by umbilical cord to placenta, the organ that develops and implants in mother's uterus during pregnancy. Through the blood vessels in umbilical cord, the fetus receives all the necessary nutrition, oxygenation and life supports from mother through placenta. Waste products and carbon dioxide from fetus are sent back through the umbilical cord and placenta to mother's circulation to be eliminated ***(Fineman et al., 2003)***.

So the placenta acts as a lung for oxygenation of fetal blood. the oxygenated blood is carried from placenta to fetus via the left umbilicalvein, it goes to liver and splits into three branches, to the hepatic vein & portal system of liver and the reminder (Slightly over half) passes through the ductus venosus intoinferior vena cava (IVC) near its junction with the right atriumso the inferior vena cava carries the oxygenated blood fromthe placenta which mixes with littleamountof deoxygenatedblood reaching the IVC from the lower1/2 of the body.

In the right atrium, most of the blood of the IVC is directed through the foramen ovale, to the left atrium. There are many factors that help the direction of the blood through the foramen ovale as the opening of the IVC faces the foramen ovale, the valve of the IVC directs the blood toward the foramen ovale and pressure