Clinical and echocardiographic study of the ductus arteriosus in preterm infants.

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Introduction

The ductus arteriosus is a wide blood vessel that connects the pulmonary artery to the aorta in the fetus. It has great importance during that stage of life because it is responsible for shunting blood away from the high-resistance pulmonary vascular bed into the systemic circulation [1].

The ductus is derived from the sixth aortic arch. The shape and size of the ductus is related to the haemodynamics in uterus. From the sixth week of fetal life, it carries most of the right ventricular output, which constitutes up to 60% of the total cardiac output. Throughout fetal life, the ductus maintains a short tubular shape, with a caliber that progressively increases with gestation to equal that of the descending aorta (10 mm) at term. At birth, the ductus undergoes rapid changes in size and shape related to the physiological process of closure. The persistent duct may, therefore, vary in morphology, but significant ducts in premature infants usually remain short and tubular. Histologically, the ductal wall is as thick as that of the aorta but has a relatively thick intima. The media contains a thick layer of smooth muscle, which, unlike the aorta, is arranged in a spiral helix that encircles the ductus in both clockwise and anticlockwise directions. This is teleologically suited for postnatal ductal closure [2, 3].

Fetal circulation

Highly oxygenated blood from the placenta enters the fetus via the umbilical vein. A proportion of this blood passes into the liver to supply the hepatic sinusoids. The remainder bypasses the liver in the ductus venosus, drains into caudal vena cava and mixes with poorly oxygenated blood returning from the fetal body. The blood in the caudal vena cava, which, although mixed is still well oxygenated, drains into the right atrium of the heart [4].

Most of the blood entering the right atrium from the caudal vena cava is directed through the foramen ovale into the left atrium where it is mixed with a small amount of deoxygenated blood returning from the lungs. The contents of the left atrium enter the left ventricle and are expelled from the heart into the aorta.

The contents of the right atrium (which consist of some well oxygenated blood from the caudal vena cava and poorly oxygenated blood returning from the head and forelimbs via the cranial vena cava) enter the right ventricle and are expelled from the heart via the pulmonary artery. Only approximately 5 -10% of the blood in the pulmonary artery enters the lungs in the fetus due to the high resistance of their non-aerated state. The remainder enters the ductus arteriosus which is a shunt linking the pulmonary artery and the aorta. The convergence of the poorly oxygenated pulmonary blood and the well-oxygenated aortic blood occurs after the main supply to the head and forelimbs have branched off the aortic arch. This ensures that the blood with higher oxygen content reaches the developing brain [4, 5].

Incidence of patent ductus arteriosus

Patent ductus arteriosus (PDA) is now the most frequent form of heart abnormality in the neonatal period, with the increasing incidence primarily resulting from the increased survival of premature infants. Approximately 10 to 70% of premature infants manifest this defect; the majority of these infants require some sort of intervention in order to close the defect [6, 7].

PDA remains a common problem for the very preterm infant. Despite being a focus of neonatal research for many years, controversy still surrounds the role of PDA in adverse outcomes and the best method and appropriate timing of treatment [8] (Table 1).

Factors maintaining ductal patency in uterus

The original view of the ductus was that it represented a relatively passive structure in uterus that was actively stimulated to contract after delivery. However, recently this theory has been changed. It has become clear that patency of the ductus in uterus is an active state. That is, it has intrinsic tone, or is topically stimulated to contract, and these procontractile

Table 1: *Incidence of PDA [9].*

Age in weeks	Incidence of PDA
28-30 wks	70-80%
31-33 wks	40-42%
34-36 wks	21%

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mechanisms are topically inhibited by vasodilators. Probably the most important dilator system identified so far is prostaglandin E2 (PGE2), which has a profound inhibitory effect on ductal smooth muscle. However, several accessory dilator systems have also been identified [10].

Prostaglandins

PGE1 and PGE2 have been found, uniformly, to be the most potent mediator, causing ductal relaxation [11].The pharmacological classification of prostanoid (P) receptors has been reviewed . Each receptor is named after the native PG that is its most potent agonist [i.e., EP for PGE1 and PGE2, IP for PGI2, DP for PGD2, FP for PGF2 and TP for thromboxane A2 (TxA2)] [12].There are at least four subtypes of EP receptors encoded by separate genes, and there are variable numbers of isoforms (depending on the species) of EP3 receptors formed by alternative messenger ribonucleic acid (mRNA) splicing from a single gene [13].

The ductus is exposed to both locally released and circulating PGs. The isolated ductus synthesizes a range of PGs. PGI2 was the main product of arachidonic acid (AA) in the ductus, but it also formed small amounts of PGE2, PGF2 , and PGD2 all about 10% the level of PGI2 synthesis , this adds further support for a physiological role for PGI2 in the control of the ductus.

The cellular sources of PGs in the ductus have been partially elucidated. In the ductus from the second trimester human fetus, PGI2 synthase was located (by immunohistochemistry) both in endothelial cells and medial smooth muscle cells, whereas in the fetal aorta, the enzyme was largely confined to the endothelium [14].

The ductus is also exposed to circulating PGE2, and it has been suggested that circulating PGE2 is more important in the control of the vessel patency than locally released PGE2 .Circulating concentrations of PGE2 increased toward term. The placenta is thought to be the major source of circulating PGE2 in the fetus. Because the lungs are the major site of PG catabolism and pulmonary blood flow is only 9% of ventricular output in the fetus, the high circulating concentrations of PGE2 are probably also related to reduced catabolism [15].

Nitric Oxide

Nitric oxide may have a role in maintaining ductal patency, immunohistochemistry studies localized endothelial nitric oxide synthase (eNOS) to the luminal endothelium and the vasa vasorum endothelium. Removing the luminal endothelium of the ductus decreased, but did not abolish, the contractile response to a NOS inhibitor, implying an extraluminal source of NOS. Both sodium nitroprusside (SNP) and glyceryl trinitrate dilate the ductus. These agents are nitric oxide (NO) donors, and they increased the intracellular concentrations of cAMP and cyclic guanosine monophosphate (cGMP) in the ductus. Inhibitors of nitric oxide synthase (NOS) promote duct contraction [16, 17].

Carbon Monoxide

The effects of carbon monoxide (CO) on the ductus have been studied for over a decade. It has been found recently that, smooth muscle of the ductus contains an enzyme, heme oxygenase, that can produce CO from heme and that the CO produced may cause vasodilatation through stimulation of cGMP or by effects on potassium channels [18].

Factors mediating contraction at birth

Although the maintenance of ductus arteriosus patency in uterus is an active state and the loss of the dilator effect of PGE2 is central to the control of the ductus in the neonate, the trigger to close the vessel after birth is more than just the withdrawal of dilator influences. The major factor actively stimulating contraction is probably the effect of increasing oxygen tension, although the isolated ductus is sensitive to a wide range of contractile agonists. The multiplicity of these contractile systems seems at odds with the relatively simple physiological role of the ductus. This can be explained by the fact that the two main systems that vary at birth, namely oxygen tension and PGE2, act synergistically to modulate the response of the ductus to vasoconstrictors.

Oxygen-induced contraction

In fetal life, the ductus is exposed to an oxygen tension that has been estimated as between 25 to 40 mmHg. After birth, the ductus is exposed to arterial blood because of the reversal of the direction of flow and arterial oxygen tension rises rapidly after delivery. Rising oxygen tension profoundly contracts the ductus. Even in full-term infants, the DA does not close immediately and, although well constricted, its patency is often apparent on echocardiography for up to, and occasionally beyond 24 hours after birth. The initial phase, or functional closure of the DA, occurs because of muscle constriction. This muscle constriction causes intimal ischemia, which in turn leads to full structural closure. In premature infants, the DA, like every organ system, is immature and not developed for this transition. As a result, the DA is more likely to remain patent and the resulting shunt may have important hemodynamic consequences [19].

Several different mechanisms have been proposed to explain the profound contractile effect of physiological increases in oxygen tension on the ductus.

Elimination of dilator prostaglandins

Loss of the dilator effect of PGE2 is central to the closure of the ductus, and treatment of the neonate with PGE2 is sufficient on its own to prevent postnatal closure. The high fetal circulating concentrations of PGE2 fall dramatically after birth. Loss of the dilator effect of circulating PGE2 has been postulated to be fundamental to the closure of the ductus. The fall in circulating concentrations of PGE2 is because of (a) the increase in lung blood flow that occurs at birth because the lungs are the major site of PG catabolism and (b) the loss of the placenta, the major source of circulating PGE2 in the fetus.

Neural vasoconstriction

The ductus arteriosus is innervated by catecholamine containing nerves. The catecholamine content of the ductus is similar to that of peripheral arteries which are known to be under autonomic neural control [20].

Other Locally Released Vasoconstrictors

The adventitia of the ductus has many mast cells present, which can release other vasoconstrictors such as histamine and 5-hydroxytryptamine both of which contracted the isolated ductus of several species [21].

Myogenic tone

The role of myogenic tone in the physiological control of the ductus is as yet obscures [22].

Circulating Vasoconstrictors

The ductus contracts in response to other circulating vasoactive agents, such as epinephrine through adrenoceptors, and bradykinin.

Ductal remodeling

As the ductus changes from an artery conveying 60% of the combined ventricular output to a permanently closed structure within a matter of hours or days, it is not surprising that the process of closure is associated with morphological changes. After birth, there is extensive remodeling of the vessel's wall, and this renders closure permanent [23].

Closure is associated with the formation of intimal cushions, which are characterized by (a) an area of subendothelial edema, (b) infolding and ingrowth of endothelial cells, and (c) migration into the subendothelial space of undifferentiated medial smooth muscle cells. Postnatal remodeling is also associated with the disassembly of the internal elastic lamina, and loss of elastin may promote smooth muscle cell migration. Some of these changes begin about halfway through gestation in humans but are much more marked after functional closure of the ductus in the neonate. Ductal remodeling may depend on ischemia of the vessel wall , but the loss of medial smooth muscle cells is by apoptosis rather than necrosis [23].

Studies employing Doppler echocardiogram and color flow mapping have indicated that functional closure of the ductus arteriosus in full term infants takes place in practically all newborns at around 72 hours of life. In preterm newborns (PT-NB), the ductus arteriosus closes a little later, taking place in the majority of those with gestational ages of more than 30 weeks by 96 hours of life. In contrast, PT-NB with gestational ages less than 30 weeks and, in particular, those who exhibit hyaline membrane disease have an increased frequency of patent ductus arteriosus (PDA) [24, 25].

Physiologic considerations of a left-to-right shunt

As with all left-to-right shunts, with PDA three major, interrelated factors control the magnitude of shunting: The diameter and length of the ductus arteriosus, which governs the resistance offered to flow; the pressure difference between the aorta and the pulmonary artery; and the systemic and pulmonary vascular resistances.

Normally after birth, systemic vascular resistance (afterload) is high, whereas pulmonary vascular resistance decreases when ventilation begins. As a result, systemic arterial blood pressure becomes higher than that in the pulmonary artery. With a small PDA, a high resistance to flow is offered by the small cross-sectional opening of the ductus arteriosus, so that the left-to-right shunt will be small despite the large pressure difference. However, with a large communication, pressures tend to become equal, and the magnitude of shunting is then determined by the relationship of the systemic and pulmonary vascular resistances. For this reason left-to-right shunting through a PDA has been defined as dependent shunting [26]. Because systemic vascular resistance does not change significantly after birth, changes in pulmonary vascular resistance are the major determinant in regulating the left-to-right shunting through a PDA. This is particularly important in the first 2 months after birth, when pulmonary vascular resistance normally is decreasing.

The physiologic features associated with left-to-right shunting through a PDA depend on the magnitude of the left-to-right shunt and the ability of the infant to handle the extra volume load. Left ventricular output, which normally is high in the immediate newborn period, is increased even further by the volume shunted left to right through the PDA. The resultant increase of pulmonary venous return to the left atrium and left ventricle increases ventricular diastolic volume (preload) and thereby left ventricular stroke volume (Frank Starling's mechanism). Left ventricular dilation will result in an increased left ventricular end-diastolic pressure with secondary increase in left atrial pressure. This may lead to signs of overt left heart failure with left atrial dilation and pulmonary edema. Right ventricular failure may occur if there is a large PDA with pulmonary hypertension or pulmonary edema and an elevated left atrial pressure, in which case pulmonary vascular resistance may be increased. The net result of both these situations is an increased pressure load for the right ventricle. Left-to-right shunting through a stretched, incompetent foramen ovale secondary to left atrial dilation is a fairly common association [27, 28].

Several compensatory physiologic mechanisms help to improve myocardial performance and thereby maintain a normal systemic output. In addition to the Frank Starling mechanism, the sympathetic adrenal system is stimulated, as is the development of myocardial hypertrophy. Increased sympathetic stimulation leads to direct stimulation of nerve fibers within the myocardium, with local norepinephrine release as well as an increase in circulating catecholamines released from the adrenal glands. As a result, both the force of contraction and the heart rate are increased. These mechanisms are responsible for the rapid heart rate and the sweating often seen in infants with heart failure. If the increased volume load persists, hypertrophy of the ventricular myocardium will develop.

These compensatory mechanisms are ordinarily well developed in older children or adults; however, they are not as well developed in newborn infants and are even less so in prematurely born infants. It is most important, therefore, to consider the state of maturity (i.e., gestational age at time of birth) of an infant who has a PDA with left-to-right shunting. Many physiologic functions that are present in older children reach full maturation at different rates and periods of gestation.

For example, sympathetic nervous innervation of the left ventricular myocardium may be completed only at term, or even after term [29]. So that in an infant born prematurely, sympathetic stimulation of the left ventricular myocardium likely would be incomplete.

The structure of the immature myocardium, too, is quite different from that at term in that there are far fewer contractile elements. Premature infants often have lower than normal serum Ca2+ concentrations, and this too may affect myocardial performance. Probably for one or all of these reasons, premature infants with left-to-right shunts through a PDA develop left ventricular failure earlier than their full-term counterparts and, in addition, with a smaller volume load. The altered myocardial structure also may be partly responsible for the poor response to digitalis of immature infants with left ventricular failure.

Of considerable importance as well is maintenance of myocardial perfusion. Because coronary arterial blood flow to the left ventricle occurs mainly during diastole and depends on the systemic arterial-intramyocardial diastolic pressure differences as well as the duration of diastole, alterations in either can affect coronary blood flow. A reduction in aortic diastolic pressure occurs in a large PDA, and with a significant shunt, left ventricular end-diastolic pressure may be increased and cause an increase in subendocardial intramyocardial pressure. The development of tachycardia will reduce the diastolic period. All three factors that affect adequate myocardial perfusion are therefore jeopardized in the presence of a large PDA [30].

Delivery of oxygen to the myocardium depends on not only the coronary blood flow, but also the oxygen content of arterial blood and the ability of arterial blood to deliver oxygen at the tissue sites. A low hemoglobin concentration caused by physiologic anemia in the newborn period, particularly in premature infants, or by repeated blood sampling as occurs with intensive neonatal care, jeopardizes oxygen delivery to the myocardium as well as to other organs. A further important factor, particularly in premature infants, is the amount of fetal hemoglobin present. Because fetal hemoglobin has a low affinity for the organic phosphates such as 2, 3-diphosphoglycerate, the facilitation of oxygen delivery to peripheral tissues is reduced. This effect is greater with higher amounts of fetal haemoglobin [31].

Diagnosis of PDA

Clinical Picture

The clinical features depend on the magnitude of left-to-right shunt through the PDA and the ability of the infant to initiate compensatory mechanisms to handle the extra volume load. Because many premature infants have respiratory distress syndrome, the stage of development of this disease and the use of surfactant replacement therapy will determine the pulmonary vascular resistance and therefore the shunt. The maturity of the infant and the stage of myocardial development determine the ability to handle the shunt. Three fairly distinct patterns of clinical presentation are recognized in these infants.

Patent Ductus Arteriosus with Little or No Lung Disease

In the first group, there is little or no underlying pulmonary disease (usually infants whose birth weight exceeds 1,500 g). However, smaller infants are encountered, and in many instances their mothers have received steroid or other therapy prior to delivery, or the infants have received surfactant replacement therapy. A systolic murmur is first heard 24 to 72 hours after birth, and as the left-to-right shunt increases, this murmur becomes louder and more prolonged, extending to and often beyond the second heart sound into early diastole. The murmur commonly is heard best at the left sternal border in the second and third intercostal spaces. The classic continuous machinery murmur, described for older children with PDA, is not usual in premature infants, in whom the murmur generally has a high-frequency quality. The pulmonic component of the second sound may become moderately accentuated.

In the most mature infants in this group, a middiastolic flow rumble owing to increased diastolic flow across the normal mitral valve may be heard at the apex. If the shunt becomes large enough, a third heart sound due to rapid ventricular filling during diastole may be heard at the apex. The pericordium becomes increasingly more hyperactive, the pulse pressure widens, and the peripheral pulses become more prominent and bounding as the left-to-right shunt increases. Increased peripheral pulses are best appreciated by the presence of palmar or forearm pulses. If the shunt is allowed to become sufficiently large, clinical evidence of left ventricular failure may appear. This includes tachycardia, tachypnea, and rales on auscultation of the lung fields. Associated with the development of pulmonary edema, there may be a decrease in arterial blood pO2. If left ventricular failure were allowed to progress, a significant number of these infants might develop episodes of apnea, often associated with severe bradycardia. Enlargement of the liver will occur, but usually quite late [32].

Patent Ductus Arteriosus in Infants Recovering from Lung Disease

The second and most common group of infants develops left-to-right shunting while recovering from severe or moderately severe respiratory distress syndrome. These infants usually weigh 1,000 to 1,500 g at birth. The idiopathic respiratory distress syndrome usually is evident within a few hours after birth, and if it follows the usual course, starts to improve after 3 to 4 days. As this improvement continues, early clinical evidence of a left-to-right shunt through a PDA appears. In addition, at about this age, fluid administration generally is increased to deliver adequate calories; this often aggravates the volume-loading effects of the left-to-right shunt on left ventricular function. Probably the ductus arteriosus has been patent since birth and the pulmonary disease with a resultant increase in pulmonary vascular resistance has prevented a detectable left-to-right shunt. As the pulmonary disease improves, oxygenation increases and the ductus arteriosus should constrict. However, most of these infants are quite immature, so a good constrictor response may not occur. Many of these infants are still maintained on mechanical ventilators

or continuous positive airway pressure (CPAP), so that careful clinical assessment is required to establish the presence of a shunt through the ductus arteriosus [33].

In many instances the murmurs are not audible until the infant is briefly detached from the ventilator or CPAP system. Because recovery from the respiratory distress syndrome often is not continuously progressive but is interspersed with periods of deteriorating lung function, left-to-right shunting (and therefore the murmur) may be intermittent for several days. The murmur commonly disappears and reappears several times within short periods of time. Initially a systolic murmur alone is heard; however, as the shunt increases, the murmur extends into diastole. The murmur is similar in distribution and quality to that in the first group of premature infants with PDA. Because infants in the second group are usually more immature than those in the first, left ventricular failure may occur in them when clinically there seems to be less left-to-right shunting. A third sound often is heard, but a middiastolic flow rumble is uncommon. The pulmonic component of the second sound ordinarily is already accentuated because of the pulmonary disease but may become louder as the shunt increases. Increasing pericordial activity is a good clinical indication of the magnitude of shunting in these infants, and increased heart rate, pulse pressure, and bounding pulses with a rapid upstroke are often detectable early. Palmar or forearm pulses are often palpable. Because most of these infants have indwelling umbilical arterial catheters, careful monitoring of the umbilical arterial blood pressure often shows a widening pulse pressure and a decrease in diastolic pressure as left-to-right shunting develops [34, 35].

Rales are unreliable as an index of pulmonary edema and left ventricular failure because they may be suppressed by positive pressure ventilation used in these infants. However, in those extubated who have recovered sufficiently from their respiratory distress syndrome, rales may be heard. Apneic episodes are also common in this group and may be associated with short periods of bradycardia.

Deterioration in the ventilatory status of an infant recovering from respiratory distress syndrome is often a strong indication of a significant left-to-right shunt through a PDA. However, other causes, such as recurring lung disease and pneumothorax or sepsis, should be actively excluded. Deterioration of the ventilatory status is manifested by the requirement for an increasing concentration of inspired oxygen, alterations in ventilator rate or pressure settings, increased requirements of CPAP, and assisted ventilation and increasing arterial blood pCO2.

Patent Ductus Arteriosus Associated with Lung Disease

The third group consists of infants who have severe respiratory distress syndrome from birth. Because many of these are extremely low birth weight infants (<1,000 g), the likelihood of a PDA being present is very high (>80%). A few show no clinical signs even when carefully evaluated for PDA. Many do show clinical evidence of a left-to-right shunt through the PDA, or fail to show improved respiratory status at an age when they should start to recover from the primary pulmonary disease. They too are extremely sensitive to small increases in Na+ and fluid administration. They require ventilatory assistance by mechanical respirators or CPAP. Deterioration commonly is manifested by the need for increasing ventilator pressure, rate, or oxygen, or CPAP support. Failure to improve is manifested by the inability to wean the infant from ventilatory support. An increase in arterial blood pCO2 is common. Murmurs may be difficult to hear, and in some of these infants the ductus arteriosus may be so widely patent that a murmur is not produced [36, 37].

Changes in the ventilatory status may be due to progression of the primary pulmonary disease, and it is often even more difficult to separate left ventricular failure from increasing pulmonary problems than in the previous group. Increasing pericordial activity, bounding pulses, and a widening arterial pulse pressure suggest the development of left-to-right shunting. When present, the murmur is usually only systolic, the pulmonic component of the second sound is accentuated, and a gallop rhythm is often heard [37].

Premature infants with clinically significant PDA are at increased risk of adverse outcomes. Left to right shunting through a PDA is associated with greater severity of respiratory distress syndrome and requires more ventilatory treatment, which increases the risk of chronic lung disease [8, 39]. Pulmonary haemorrhage [40] intraventricular hemorrhage, necrotizing enterocolitis [41] and retinopathy of prematurity [42].

PDA also adversely affects blood pressure, [43] the systemic perfusion patterns to many organ systems, [44] and is associated with an increased risk of intraventricular hemorrhage or ischemic cerebral damage [45, 46] and necrotizing enterocolitis. The effects of surfactant replacement on pulmonary vascular resistance lead to the clinical emergence of PDA earlier and more frequently in preterm infants [47].

Investigations

Chest X rays

Chest X rays may reveal cardiomegaly, pulmonary plethora, both left atrial and left ventricular enlargement and perihilar edema. Also an enlarged aortic knob is very specific radiological finding of PDA. However chest radiography plays minimal role in the diagnosis of patent ductus arteriosus in premature infants with hyaline membrane disease. Reported radiographic criteria are difficult to apply in these patients. Cardiac size varies with mechanical ventilation and the degree of hypoxia and acidosis. Hyaline membrane disease and associated lung diseases mask the appearance of pulmonary edema [48].

Echocardiography

Echocardiography is a unique noninvasive method for imaging the living heart. It is based on detection of echoes produced by a beam of ultrasound (very high frequency sound) pulses transmitted into the heart.

Accurate diagnosis of a PDA requires echocardiography. Echocardiography together with Doppler and color Doppler allows assessment of patency, diameter of the DA (using

color Doppler), and direction of the shunt (using color and pulsed Doppler). Pulsed Doppler technology allows accurate assessment of the velocity and direction of the shunt through the cardiac cycle. The direction of flow varies from blood shunting predominantly left to right, to bidirectional and predominantly right to left. Pulsed Doppler also allows assessment of disturbances to blood flow on either side of the DA. Specifically, it reveals increased diastolic forward flow in the left pulmonary artery or retrograde diastolic flow in the post ductal descending aorta. Both of these phenomena are useful markers of hemodynamic DA significance [49].

Historically, a variety of indirect echocardiographic measures, such as the left atrial to aortic root ratio, have been used to diagnose and quantify the size of a PDA. With modern ultrasound technology, these markers have become less useful, except where direct imaging is not possible. Direct imaging is now the method of choice both to diagnose patency and determine the significance of the DA.

Clinically significant PDA is difficult to diagnose accurately in early postnatal life [50]. Therefore, echocardiography has become essential in the evaluation of clinically significant ductal shunting [51].

Patency can be confirmed by diastolic turbulence on Doppler in the pulmonary artery. (Figure 1) below contrast the normal Doppler pattern in the pulmonary artery (A) with the turbulent pattern seen with a patent duct (B). This is a highly accurate method for diagnosing ductal patency but tells you little about the haemodynamic significance [52].

Shunt direction is demonstrated with pulsed wave and colour Doppler. There are broadly three direction patterns which are shown below in (Figure 2). Pure left to right (A), bidirectional (B) and right to left (C). Most babies even in the early hours after birth have left to right or bidirectional with a dominant left to right component. Predominantly right to left shunting is unusual.

Haemodynamic significance is confirmed by diameter (>1.5mm) and absent or retrograde diastolic flow in the postductal aorta. (Figure 3) below contrast two preterm ducts in the first hours after birth. (A) is well constricted at less than 1.0mm diameter, much as you would see in a term baby. Constriction has failed in (B) which is 2.0mm in diameter and a large left to right shunt draining blood from the systemic circulation is already present [52].

Echocardiography has shown that four patterns of PDA shunt flow can be identified using pulsed Doppler echocardiography, and the longitudinal observation of the change in Doppler pattern can provide an understanding of the haemodynamics of ductal shunting and is useful for the prediction of risk of clinically significant PDA [53,54].

Pulmonary hypertension pattern

A bi-directional shunt is noted in the profile; a right to left shunt (downward away from the baseline) in early systole was followed by a small left to right shunt (upward away from the baseline) throughout the diastole. This pattern was seen in early postnatal life in the presence of high pulmonary vascular resistance (Figure 4.a).

Growing pattern

A bi-directional shunt still could be noted, but the right to left shunt decreased and a growing left to right shunt was seen in the profile. This pattern represents a growing left to right shunt through a large ductus accompanying a fall in pulmonary vascular resistance (Figure 4.b).

Pulsatile pattern

No right to left shunt was noted in the profile, and a much greater left to right shunt was shown by a pulsatile flow of peak velocity of about 1.5 meters/seconds (Figure 4.c).

Closing pattern

The prominent difference between this and the pulsatile pattern is that the closing pattern did not show the rhythmically pulsatile change, but rather a continuous left to right shunt with a peak flow velocity of about 2 milliseconds covering the whole cardiac cycle in the profile. According to the Bernoulli equation, this pattern implies that a shunt flows through a constrictive ductus to produce a high flow velocity (Figure 4.d).

Closed pattern

This pattern had to be sampled in the pulmonary artery, because the Doppler gate was placed in the pulmonary end of the ductus while it was closed, so true ductal sampling would have produced no Doppler signal at all. Thus the closed pattern is similar to the pulmonary artery flow pattern, and was taken to show the contrast with the PDA patterns (Figure 5).

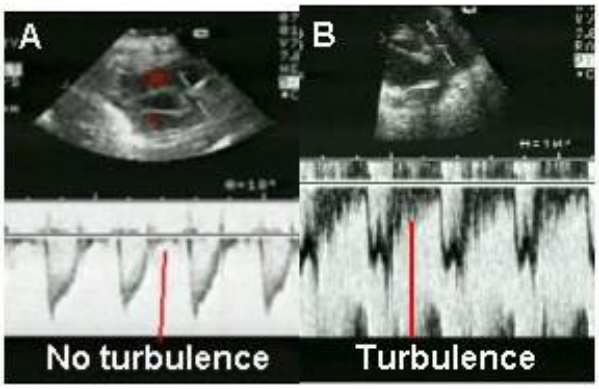

Figure 1: *Doppler Ultrasound Patterns in the Pulmonary Artery for Assessing Ductal Patency.*

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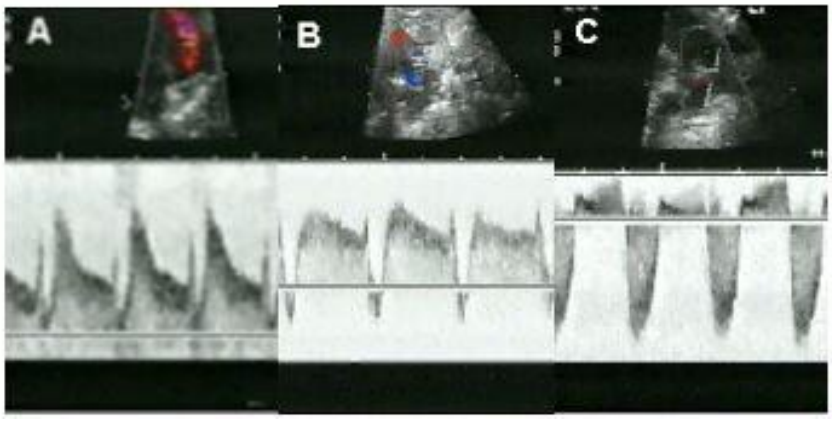

Figure 2: *Shunt Direction Patterns in the Pulmonary Artery Demonstrated by Pulsed Wave and Color Doppler.*

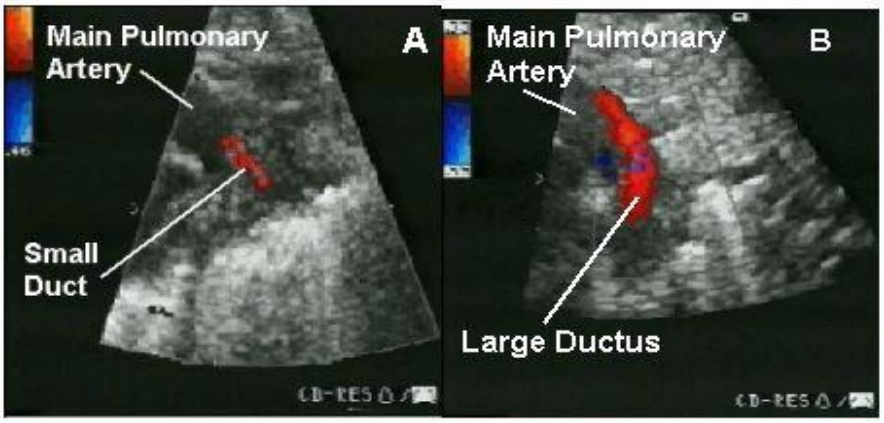

Figure 3: *Hemodynamic Significance of Ductal Patency Assessed by Ductal Diameter and Diastolic Flow in the Postductal Aorta.*

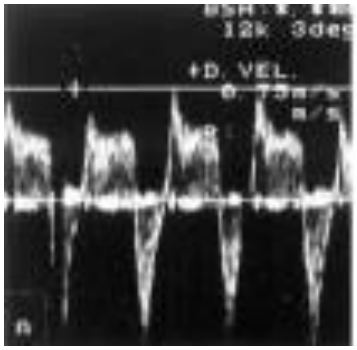

Figure 4.a: *Characterization of Early Postnatal Bi-Directional Shunt Patterns Due to Elevated Pulmonary Vascular Resistance.*

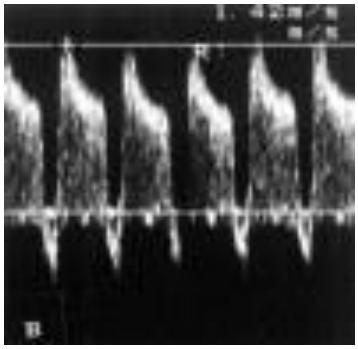

Figure 4.b: *Progressive Left-to-Right Shunt Development with Decreasing Pulmonary Vascular Resistance in Neonatal Circulation.*

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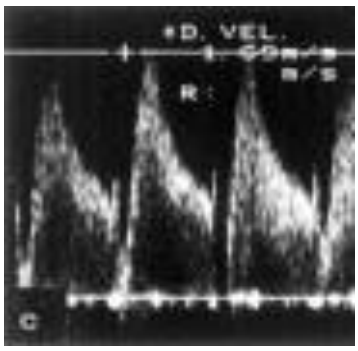

Figure 4.c: *Absence of Right-to-Left Shunt and Increased Left-to-Right Shunt with Pulsatile Flow in Neonatal Circulation.*

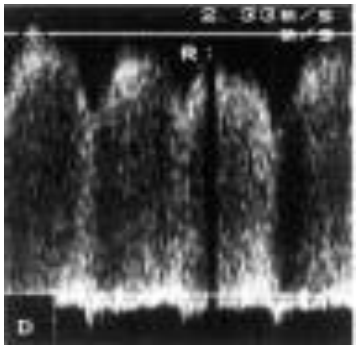

Figure 4.d: *Continuous Left-to-Right Shunt through Constrictive Ductus: A Non-Pulsatile High-Velocity Flow Pattern in Neonatal Circulation.*

Figure 5: *Pulmonary Artery Flow Pattern in Closed Ductus Arteriosus: Doppler Sampling to Differentiate from Patent Ductus Arteriosus (PDA) Profiles.*

Plasma b-type natriuretic peptide

Recently measurement of plasma B-type natriuretic peptide (BNP) as early as the third day of life predicts those preterm infants who will have a haemodynamically significant PDA at the end of the first week. This suggests that the test may complement echocardiography as an early indicator of the need to treat the PDA [55].

Treatment of PDA

When to treat a PDA remains controversial. There are 3 broad approaches to the timing of PDA treatment that include the following:

1. Prophylactic treatment.
2. Presymptomatic treatment.
3. Treatment when clinically symptomatic.

None of these approaches has shown clear benefits in short- and long-range outcomes.

Prophylactic treatment

This involves the administration of indomethacin or ibuprofen to all high-risk infants on the first day usually within the first 6 hours. There have been several randomized trials addressing this approach. Indeed, prophylactic administration of indomethacin in preterm infants prior to 28 weeks decreases the incidence of serious pulmonary hypertension, grade III/ IV intraventricular hemorrhage, and need for surgical closure, but has not been shown to alter mortality [56, 57].

Prophylactic treatment with indomethacin has a number of immediate benefits, in particular a reduction in symptomatic patent ductus arteriosus, the need for duct ligation and severe intraventricular hemorrhage. There is no evidence to suggest either benefit or harm in longer term outcomes including neurodevelopment. Depending on clinical circumstances and personal preferences, there may be a role for prophylactic indomethacin in some infants on some neonatal units [58, 59].

Prophylactic ibuprofen also decreases the need for symptomatic treatment but has not yet been shown to alter the incidence of intraventricular haemorrhage [60]. In addition, one trial reported an incidence of significant pulmonary hypertension after prophylactic ibuprofen administration [61].

Pre-symptomatic Treatment

This approach involves using a variety of diagnostic methods, clinical and echocardiographic, to detect ducts in the pre-symptomatic period and then closing at this time. The timing of the interventions in these trials was usually between 24 hours and day 5 of life. There is a significant decrease in the incidence of symptomatic PDA following treatment of an asymptomatic PDA with indomethacin. There is also a small but statistically significant decrease in the duration of requirement for supplemental oxygen. There are no reported long term outcomes in the included trials, and so it is not possible to comment on possible long term effects. Further studies are required to determine the long term benefits or harms of closing a PDA prior to the onset of symptoms [62].

Treating Clinically Apparent Patent Duct

Using this approach, about a third of babies born before 30 weeks will need treatment. Although widely used, there is no evidence that this approach improves outcomes. In all the randomized trials the control groups had backup treatment options which meant in babies randomized to placebo, the ducts were closed only shortly after the treatment groups. The national collaborative trial was the largest of these and this study did show there was no benefit in treating the duct as soon as it becomes clinically apparent as opposed to waiting a day or two [63].

The lines of treatment of PDA include both medical, surgical and non-surgical approach for closure of the PDA [64].

The medical lines involved in closure of the PDA are fluid restriction, the use of diuretics, inotropic agents in case of occurrence of heart failure and the administration of prostaglandins synthase inhibitors (indomethacin, or ibuprofen). Also of vast importance is correction of anemia, general supportive measures to vital systems [65].

The first step to be considered in management of PDA is restricting 10-20% of the total volume administered to the newborn. Where excessive fluid administration has been associated with increase incidence of PDA, also this restriction will act to cause decrease in pulmonary venous pressure, which increase lung compliance and promote weaning from ventilator [66]. Such restriction is monitored through the body weight, serum electrolytes, urine output and specific gravity.

Furosemide, a loop diuretic, is the main diuretic used in cases of PDA. It acts to decrease the volume imposed on the cardiac chambers, given in a dose of 1-2 mg/kg/dose, every 12 hrs, or according to clinical situation. Dehydration state, serum electrolytes should be closely monitored with the use of furosemide. There is not enough evidence to support the administration of furosemide to premature infants treated with indomethacin for symptomatic patent ductus arteriosus. Furosemide appears to be contraindicated in the presence of dehydration in those infants [67].

Digoxin is the main inotropic agent used in case of heart failure caused by haemodynamically significant PDA, it has a mechanical function on cardiac muscle, where it increases the cardiac contractility by increasing interaction between actin and myosin filament in cardiac sarcomere [68]. When using digoxin electrolytes should be monitored closely, in addition observing for the occurrence of digoxin induced arrhythmias.

Indomethacin

Indomethacin is the most widely used prostaglandin synthetase inhibitor for the pharmacological closure of PDA. The response to oral or rectal indomethacin therapy is highly variable, with an overall response rate of about 60 % [69]. Intravenous indomethacin therapy has a higher and more consistent success rate of about 90% (range 75-96%). Absorption of orally administered indomethacin is relatively poor, and the variability in serum levels is greater with oral compared with intravenous therapy. The rate of PDA closure with indomethacin therapy improved following the change to the intravenous route [70]. Treatment failure was confined to therapy after one week of age. It has been shown the poorer response in older infants is the result of pharmacokinetic differences at a greater postnatal age, and a larger dose or an increased number of doses may be required to achieve the same closure rate as in younger infants [71].

Indomethacin traditionally was given at 0.2 mg/kg 12 hourly for 3 doses. Two randomized trials suggested that 0.1 mg/kg daily for 6 days achieved similar closure rates with fewer side effects [72,73]. More recently, some studies showed that 0.2 mg/kg followed by 2 doses of 0.1 mg/kg at 12 hourly intervals was as effective as the 6 daily doses of 0.1 mg/kg, with no difference in side effects [74]. Giving each dose as an infusion over 20 to 60 minutes appears to limit some of the negative effects on organ blood flow [75]. The immediate constrictive effect of indomethacin varies, but there is a measurable and significant response by 2 hours after the first dose.(76) Indomethacin therapy was found to be successful in 90% of infants <1500 g birthweight after the first course with a recurrence rate of 3% [77].

Adverse Effects of Treatment

The renal blood flow velocity decreases for about two hours [78] and dilutional hyponatraemia can result from a transient reduction in glomerular filtration rate and free water clearance [79]. Frusemide given with indomethacin can prevent the reduction in urine output without affecting its therapeutic effectiveness [80], but this is contraindicated in the presence of dehydration. Low-dose dopamine has not been shown to reduce the magnitude of oliguria [82]. Indomethacin is not contraindicated in infants with high serum creatinine and blood urea nitrogen levels, because they are often secondary to poor renal perfusion in infants with PDA and would improve following closure of the PDA with indomethacin therapy. Coagulation defects should be corrected before giving indomethacin, as it impairs synthesis of thromboxane

A2, a potent inducer of platelet aggregation, and causes prolongation of the bleeding time.

Indomethacin, though protein bound, does not affect the binding of bilirubin to protein and is safe to use in jaundiced infants [83]. Although one study suggested that indomethacin predisposes the preterm infant to the development of sepsis, this association has not been observed in other studies [84].

Gastrointestinal complications are associated with serious morbidity and mortality. The disturbance in mid-gut perfusion in PDA is known to be exacerbated by indomethacin [85], although this can be minimized with a slow infusion over 30 minutes [86]. A study in infants <1000g birthweight has shown that when indomethacin was given as a slow infusion, the incidence of bowel perforation and NEC in infants treated for a PDA was not significantly different from infants without a PDA and not given indomethacin [77] . NEC following indomethacin therapy is seen only in the early treatment . To avoid NEC with early indomethacin therapy, it has been suggested that the 0.1 mg/kg doses be discontinued as soon as the PDA has closed (mean cumulative dose at ductal closure was 0.35 mg/kg in that study), [76] or that a continuous but slow infusion of indomethacin (0.004 mg/kg/h) be given until ductal closure [87]. Indomethacin increases systemic blood pressure [88] but causes a significant reduction in flow velocity in the anterior cerebral artery [89], which can be minimized with a slow infusion [90, 91]. Indomethacin has been shown to improve cerebral auto regulation so that cerebral oxygen metabolism is not compromised even at low cerebral perfusion pressures [92]. A large RCT of early prophylactic indomethacin has reported a reduction in the incidence of PDA and severe periventricular haemorrhage [93]. The latter finding could be explained by the fact that early ductal closure with indomethacin results in improved stability of arterial blood gases and systemic blood pressure, which predispose to periventricular hemorrhage in preterm infants [94].

Ibuprofen

This is a non-steroidal anti-inflammatory agent which has been shown to be effective in closing the PDA but without affecting intestinal haemodynamics [95, 96]. It does not have a direct effect on cerebral and renal blood flow velocities, and haemodynamic changes are related to closure of the ductus induced by the drug [97]. Ibuprofen is given intravenously at a dose of 10 mg/kg followed by 5 mg/kg 24 and 48 hours later. A RCT has shown that it is as efficacious as indomethacin and is significantly less likely to induce oliguria [98]. However, this comparison was made with an indomethacin regime of 0.2 mg/kg at 12-hour intervals for three doses, and it is known from another RCT that an indomethacin regime of 0.1 mg/ kg at 24-hour intervals for six doses results in a higher ductal closure rate with less renal side effects.(73) Comparison of ibuprofen with this prolonged low-dose indomethacin regime has not been done. Day one prophylactic ibuprofen has been compared in a RCT with later expectant treatment for PDA diagnosed by echocardiography [99]. Unlike when indomethacin was given prophylactically, early ibuprofen did not result in significant adverse effects.

Sulindac

This is a relatively renal-sparing cyclo-oxygenase prostaglandin inhibitor that has comparable anti-inflammatory property and potency to indomethacin. The limited clinical experience with sulindac, given orally at a dose of 3 mg/kg every 12 hours for four doses, suggested that it is as effective as indomethacin in closing PDA but without compromise of the renal function [100]. However, its spectrum of gastrointestinal complications is similar to those described for indomethacin, and one infant was reported to have died from hemorrhagic gastritis following sulindac therapy [101]. Until the question of safety could be adequately addressed, the use of sulindac in the treatment of PDA should remain experimental.

Use of Indomethacin versus Ibuprofen

Both work by a general inhibition of prostaglandin synthesis. Indomethacin has been used for many years and will close the duct in most cases but at the expense of some worrying side effects including reduced cerebral blood flow [102], oliguria, hyponatraemia and gastro-intestinal complications. Infusing the dose over 20 to 30 minutes may reduce but does not eliminate the effect on cerebral blood flow [103]. Two randomized trials have shown that a dose of 0.1mg/kg daily for 6 days is as effective as the traditional 0.2mg/kg 12hrly for three doses but causes less side effects [104]. However, a more recent trial using 0.2mg/kg followed by two lower doses at 0.1mg.kg showed no advantage to a longer course [105]. Because of side effects, Ibuprofen has been suggested as an alternative to indomethacin. Randomized trials have shown it to have similar efficacy in closing the duct with a lower rate of side effects [106,107]. Furthermore, blood flow studies have shown that ibuprofen does not have the negative effects on cerebral blood flow [108]. In Egypt the lack of a commercially available parenteral preparation is one of the major obstacles to its wider use and because of this we continue to use indomethacin. Should a parenteral preparation become available, the recent evidence would support the use of ibuprofen in preference to indomethacin.

Surgical Treatment

The use of surgical ligation as a first line of treatment for PDA is influenced mainly by surgical availability. There is no evidence to support surgery as the preferable treatment approach. A single randomized controlled trial, known as the Collaborative trial, evaluated 405 infants of <1,750 g birth weight. Infants randomized to surgery had higher rates of pneumothorax and retinopathy of prematurity but no difference in other outcomes, including mortality. Cassady et al randomized infants to early prophylactic ligation, and the group with early DA ligation had a lower rate of necrotizing enterocolitis but no differences in other outcomes, including chronic lung disease and mortality [109]. In many neonatal intensive care units (NICUs), surgical ligation is reserved for infants with a symptomatic PDA that has failed to close with medical treatment.

Surgical ligation of PDA is usually seen as the option when medical management has failed or is contra-indicated..

Complications of standard surgical PDA ligation are almost always related to the left lateral thoracotomy. Recanalization of the duct has been reported but rarely following ligation. Inadvertent ligation of the left pulmonary artery and the descending aorta has both been reported, as has the unmasking of a coarctation following ligation of a large PDA. However, complications are rare and any early operative mortality is usually associated with other complications of prematurity [110]. It is important to realize that thoracotomy and lung retraction may have short-term adverse effects upon ventilation. Video-assisted thoracoscopic PDA clipping [111] and catheter PDA occlusion are newer techniques used successfully in older, larger children. Whilst some premature infants have also been treated thoracoscopically, this is not yet widely available or practiced. Catheter PDA 'coil' occlusion is usually only practiced upon larger infants, but is an option for those ducts that remain patent throughout infancy but which have not required surgical intervention.

All of these factors lead us to postulate that the presence of PDA may cause echocardiographic alterations that would precede the clinical manifestations. The present study was therefore designed with the objective of analyzing the relationship between the echocardiographic findings in patent ductus arteriosus and the presence of clinical signs in preterm newborns.

Aim of the work

This work had the following objectives

1. To study the correlation between clinical and echocardiographic findings in cases of PDA in preterm newborns.
2. To assess the reliability of clinical examination in detecting significant PDA in preterm newborns.

Patients and methods

The study included 61 preterm newborns admitted to NICU at Alexandria University Children's Hospital.

The babies were divided into three groups according to birth weight

1. Group A: those with birth weight more than 2000 gm.
2. Group B: those with birth weight from 1000 ≤ 2000 gm.
3. Group C: those with birth weight less than 1000 gm.

Newborns with major congenital anomalies, complex congenital heart diseases and those who died before initial or follow up echocardiography were excluded.

Every case in the study was subjected to the following

1. Full history taking including antenatal and perinatal history.
2. Thorough clinical examination stressing on the cardiovascular system, especially presence of
    a. Tachycardia (> 170 beats/minute)
    b. Visible pericordial activity.
    c. Heart murmur.
    d. Bounding pulsations (radial, femoral, posterior tibial and dorsalis pedis).
    e. Wide pulse pressure (systemic arterial pressure in mmHg, measured with an oscillometric, noninvasive method in the four limbs). Pulse pressure Considered wide if more than 30 mmHg.

The physical examination of the PT-NB was performed by a neonatologist, a member of the nursery's own treatment team, who was unaware of the echocardiogram results.

It was done initially in the first three days of life and repeated daily in the first week.

1. Chest x ray.
2. Monitoring oxygen saturation by pulse oximetry.
3. Echocardiographic evaluation using Sonoace 8000 Ex-prime manufactured by Medison.Probe P3-7AC was the probe used (multiple frequencies 5.5- 7.5 MHz). Echo done on the third day of life (Echo 1) repeated in cases with PDA early on the second week (Echo2) and on the third week (Echo 3).

Such evaluation aimed to detect the following data

a). Patency of the duct.

b). Internal ductal diameter.

c). Maximal shunt velocity.

d). Ratio of the diameter of left atrium to aortic root.

Results

This study included 61 preterm newborns admitted at NICU, Alexandria University Children's Hospital. All had respiratory distress of variable etiology (TTN, RDS and neonatal pneumonia). The characteristics of the newborns evaluated in this study are described in (Table 2). Seventeen NB were more than 2 kg (group A), 26 were 1-2 kg (group B), and 18 were less than 1 kg (group C). The studied groups included 28 males (45.9%) and 33 females (54.1%).The mode of delivery was NVD in 30 cases (49.2%), and C.S in 31 (50.8%). The mean gestational age in group A was 34.94 wks ranged from 34 to 36, that of group B was 32.88 wks ranged from 30 to 36 , and in group C it was 29.2 wks ranged from 27 to 33 wks. (Table 3) & (Figure 6) show the incidence of PDA in Echo 1, Echo 2 and Echo 3. Forty cases had pPDA in Echo 1 (65%), with the highest incidence in group C (77.8%), less in group B (65.4%), and the least incidence in group a (53%). Twelve cases had pPDA in Echo 2 (19.6%) and only 5 cases had pPDA in Echo 3 (8.1%). (Table 4) shows the use of prostaglandin inhibitors in the different groups, 7 cases (all in group C) received prophylactic indomethacin (11.5%). Seventeen cases in all groups received therapeutic indomethacin (27.9%) and 2 cases received therapeutic oral ibuprofen (3.3%).

(Table 5) & (Figure 7) show the comparison between cases with PDA vs. cases with early spontaneous duct closure in Echo 1, regarding some maternal risk factors. No significant differences were found between the studied groups with regards to these factors.

Table 2: *Descriptive data of the studied groups.*

Characteristics	Group A (17) "wt > 2kg"		Group B (26) "wt 1≤2kg"		Group C (18) "Wt < 1 kg"		Total (61)	
	No.	%	No.	%	No.	%	No.	%
Sex								
Male	5	45.9	13	50.0	10	55.6	28	45.9
Female	12	54.1	13	50.0	8	44.4	33	54.1
Delivery								
NVD	11	64.7	13	50.0	6	33.3	30	49.2
C.S.	6	35.3	13	50.0	12	66.7	31	50.8
AgA	16	94.1	20	76.9	11	61.1	47	77
SGA	1	5.9	6	23.1	7	38.9	14	22.9
Cause of respiratory distress								
TTN	7	41.2	9	34.6	1	5.6	17	27.8
Neonatal pneumonia	9	52.9	11	42.3	2	11.1	22	36.1
R.D.S	1	5.9	6	23.1	15	83.3	22	36.1
Method of oxygenation								
Head box	8	47.1	12	46.1	2	11.1	22	36.1
CPAP	4	23.5	8	30.8	3	16.7	15	24.6
IPPV	5	29.4	6	23.1	13	72.2	24	39.3

Table 3: *Incidence of PDA in Echo 1, 2 and 3.*

Ductal patency in Echo	Group A (17) "wt > 2kg''		Group B (26) "wt 1≤ 2kg"		Group C (18) "Wt < 1 kg"		Total 61	
	No.	%	No.	%	No.	%	No.	%
Echo 1	9	53	17	65.4	14	77.8	40	65.5
Echo 2	3	17.6	7	26.9	2	11.1	12	19.6
Echo 3	1	5.9	3	11.5	1	5.6	5	8.1

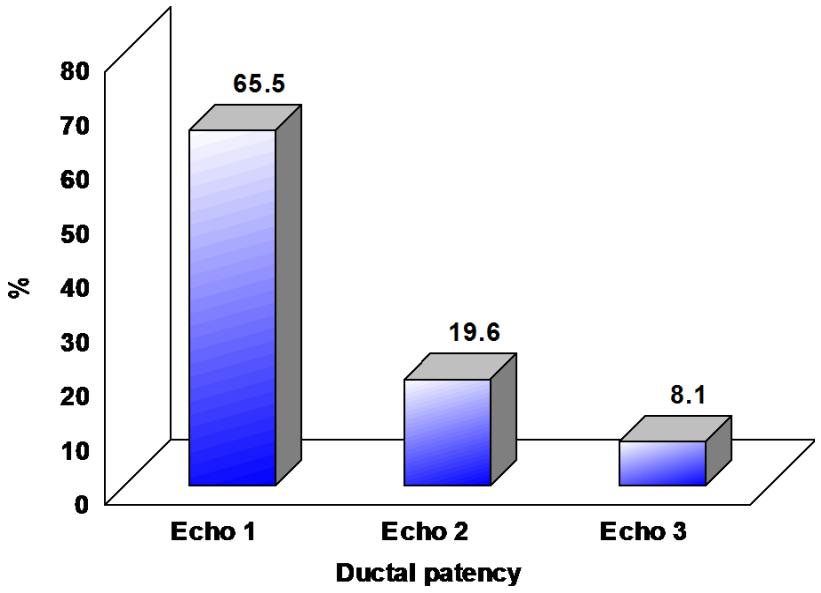

Figure 6: *Incidence of PDA in Echo 1, 2 and 3.*

Table 4: *The use of prostaglandin inhibitors in the different groups.*

Prostaglandin inhibitors	Group A (17) "wt > 2kg"		Group B (26) "wt 1≤ 2kg"		Group C (18) "Wt < 1 kg"		Total (61)	
	No.	%	No.	%	No.	%	No.	%
Prophylactic indomethacin	-	-	-	-	7	38.9	7	11.5
Therapeutic indomethacin	4	32.5	8	30.7	5	27.7	17	27.9
Therapeutic Ibuprofen	-	-	2	7.6	-	-	2	3.3

Citation: *Taha A. S. Clinical and echocardiographic study of the ductus arteriosus in preterm infants. J Preg Neonatal Med. 2024;8(5):221*

Table 5: *Maternal risk factors in neonates with PDA and neonates with closed duct in Echo 1.*

Maternal risk factors	Neonates with patent duct in Echo 1 "n=40"		Neonates with closed duct in Echo1 "n=21"		X2-test p
	No.	%	No.	%	
Caesarean section delivery	19	47.5	11	52.4	0.717
Preterm labour pain	12	30	5	23.8	0.608
Pre-eclampsia	8	20	7	33.3	0.251
Diabetic mother and gestational diabetes	4	10	1	4.8	0.47
PROM	6	15	3	14.3	0.94
Antepartum hge	8	20	1	4.8	0.11
Antenatal corticosteroids	1	2.5	1	4.8	0.637
UTI	1	2.5	2	9.5	0.22
Twin pregnancy	8	20	2	9.5	0.252
Positive consanguinity	10	25	2	9.5	0.14
P* is significant if< 0.05					

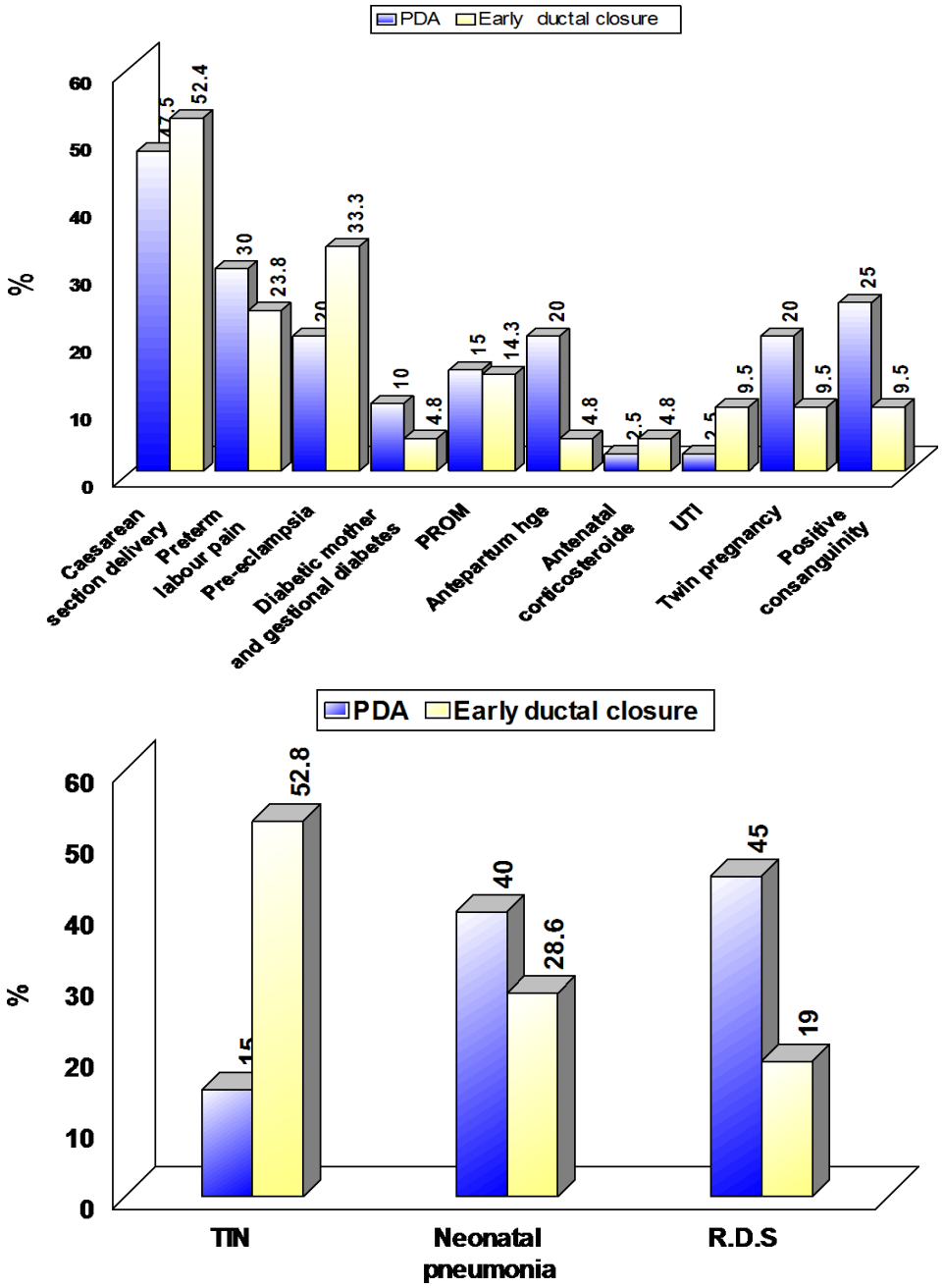

Figure 7: *Maternal risk factors in neonates with PDA and neonates with closed duct in Echo 1.*

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(Table 6) & (Figure 8, 9) compared neonates with early ductal closure vs. neonates with PDA in Echo 1, regarding causes of respiratory distress and the method of oxygenation. Early ductal closure was significantly higher among TTN cases, while ductal patency was significantly higher among RDS and pneumonia cases.

Regarding the method of oxygenation, early ductal closure was significantly higher among neonates on head box, while ductal patency was significantly higher among neonates on IPPV. No statistically significant difference was detected between both groups among neonates on CPAP.

(Table 7) & (Figure 10) compared pertinent clinical signs of patent ductus between neonates with PDA in echo 1 (40 cases) vs. those with pPDA (12cases) in Echo 2. It revealed that in cases with PDA in Echo1, 8 cases (20%) had tachycardia, 11 (27.5%) had visible pericordial pulsations, 5 (12.5%) had bounding pulsations, 6 (15%) had wide pulse pressure, 8 (20%) had murmur and 2 (5%) had hepatomegaly. In cases with pPDA in Echo 2 there were 7 cases (58.3%) had tachycardia, 9 (75%) had visible pericordial pulsations, 10 (83.3%) had bounding pulsations, 10 (83.3%) had wide pulse pressure, 11 (91.7%) had murmur, and 4 (33.3%) had hepatomegaly. Both groups differs significantly regards all clinical sings.

(Tables 8, 9, 10, 11 & 12) correlate ECHO 1 findings with clinical signs of PDA in the first 3 days. Table 6 compared echocardiographic findings in PDA cases with tachycardia vs. those without tachycardia, the difference in the duct diameter and left atrium to aortic root ratio were statistically significant while the difference in the maximal shunt velocity was not. Table 7 compared echocardiographic findings in PDA cases with vs. those without visible pericordial activity. The differences in duct diameter, maximum shunt flow velocity and left atrium to aortic root ratio were statistically significant. Table 8 compared echocardiographic findings in PDA cases with vs. those without bounding pulsations. The difference in duct diameter was statistically significant while the differences in the maximal shunt velocity and left atrium to aortic root ratio were not. Table 9 compared echocardiographic findings in PDA cases with vs. those without wide pulse pressure. The difference in duct diameter was statistically significant while the differences in the maximal shunt velocity and left atrium to aortic root ratio were not. Table 10 compared echocardiographic findings in cases with vs. those without murmur; the difference in maximum shunt velocity was statistically significant, while the differences in duct diameter and left atrium to aortic root ratio were statistically insignificant.

In (Table 13) the forty cases that had PDA in Echo 1 were classified into two groups according to duct closure in the follow up. Group with closed PDA in Echo 2 vs. those with pPDA in Echo 2, these two groups were compared regarding Echo 1 findings. The differences between both groups were statistically significant regards duct diameter and maximal shunt velocity only.

Table 6: *Comparison between neonates with patent duct versus neonates with closed duct in Echo 1, regarding the cause of respiratory distress and the method of oxygenation.*

	Neonates with patent duct in Echo 1 "n=40"		Neonates with closed duct in Echo 1 "n=21"		X2-test p
	No.	%	No.	%	
Cause of respiratory distress TTN	6	15	11	52.8	0.0013*
Group A (n=17)	2	11.76	5	29.4	0.039*
Group B (n=26)	4	15.4	5	19.2	0.16
Group C (n=18)	0	0	1	5.6	0.11
Neonatal pneumonia	16	40	6	28.6	0.045*
Group A (n=17)	6	35.3	3	17.6	0.039*
Group B (n=26)	8	30.8	3	11.5	0.21
Group C (n=18)	2	11.1	0	0	0.04*
R.D.S	18	45	4	19	0.001*
Group A (n=17)	1	5.9	0	0	0.11
Group B (n=26)	5	19.2	1	3.8	0.036*
Group C (n=18)	12	66.7	3	16.7	0.001*
Method of oxygenation Head box	9	22.5	13	61.9	0.048*
Group A (n=17)	3	17.6	5	29.4	0.042*
Group B (n=26)	5	19.2	7	26.9	0.21
Group C (n=18)	1	5.6	1	5.6	0.99
CPAP	10	25	5	23.8	0.46
Group A (n=17)	2	11.8	2	11.8	0.78
Group B (n=26)	6	23.1	2	7.7	0.013*
Group C (n=18)	2	11.1	1	5.9	0.29
IPPV	21	52.5	3	14.3	0.001*
Group A (n=17)	4	23.5	1	5.9	0.31
Group B (n=26)	6	23.1	0	0	0.0031*
Group C (n=18)	11	61.1	2	11.1	0.012*
P* is significant if< 0.05					

Citation: *Taha A. S. Clinical and echocardiographic study of the ductus arteriosus in preterm infants. J Preg Neonatal Med. 2024;8(5):221*

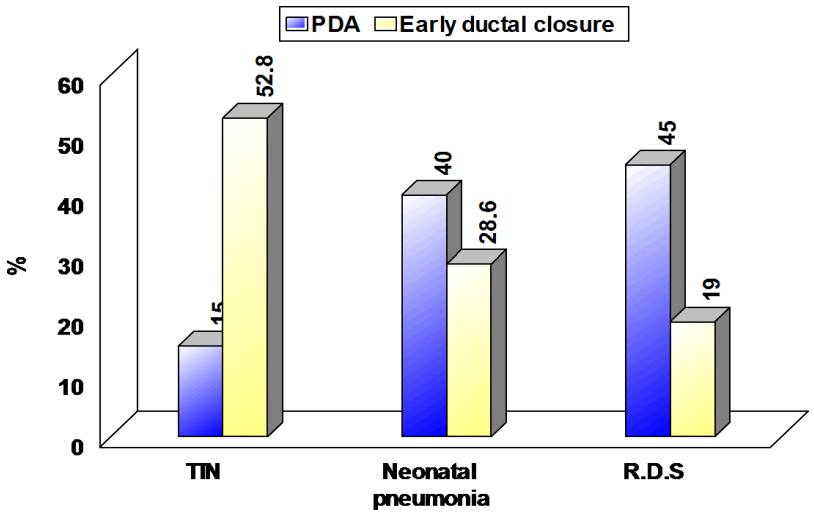

Figure 8: *Comparison between neonates with early ductal closure vs. those with PDA in Echo 1, regarding the cause of respiratory distress.*

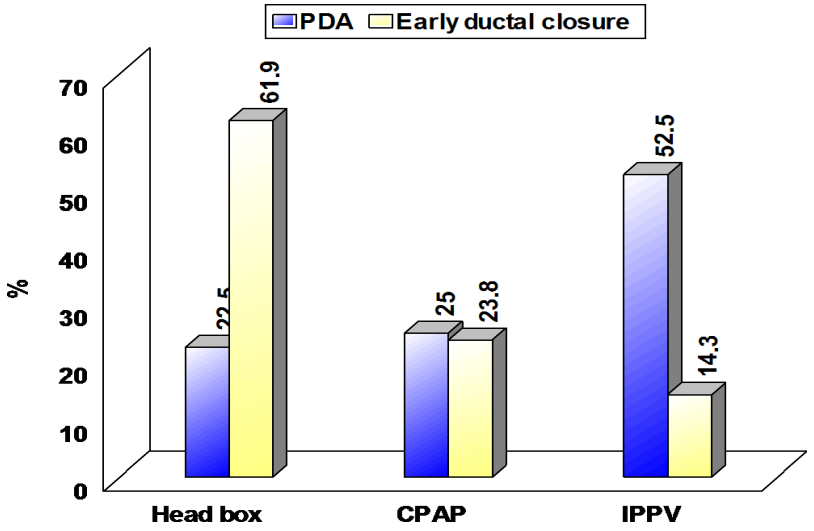

Figure 9: *Comparison between neonates with early ductal closure versus those with PDA in Echo 1, regarding the method of oxygenation.*

Table 7: *Comparison between pertinent clinical sings in cases with PDA in Echo 1 vs. those with pPDA in Echo 2.*

Clinical signs of PDA	PDA in Echo 1 "n = 40"		pPDA in Echo 2 "n = 12"		X2-test P
	No.	%	No.	%	
Tachycardia					
Yes	8	20	7	58.3	0.032*
No	32	80	5	41.7	
Visible pericordial pulsation					
Yes	11	27.5	9	75	0.01*
No	29	72.5	3	25	
Bounding pulsation					
Yes	5	12.5	10	83.3	0.001*
No	35	87.5	2	16.7	
Wide pulse pressure					
Yes	6	15	10	83.3	0.0021*
No	34	85	2	16.7	
Murmur					
Yes	8	20	11	91.7	0.0011*
No	32	80	1	8.3	
Hepatomegaly					
Yes	2	5	4	33.3	0.0046*
No	38	95	8	66.7	
P* is significant if< 0.05					

Citation: *Taha A. S. Clinical and echocardiographic study of the ductus arteriosus in preterm infants. J Preg Neonatal Med. 2024;8(5):221*

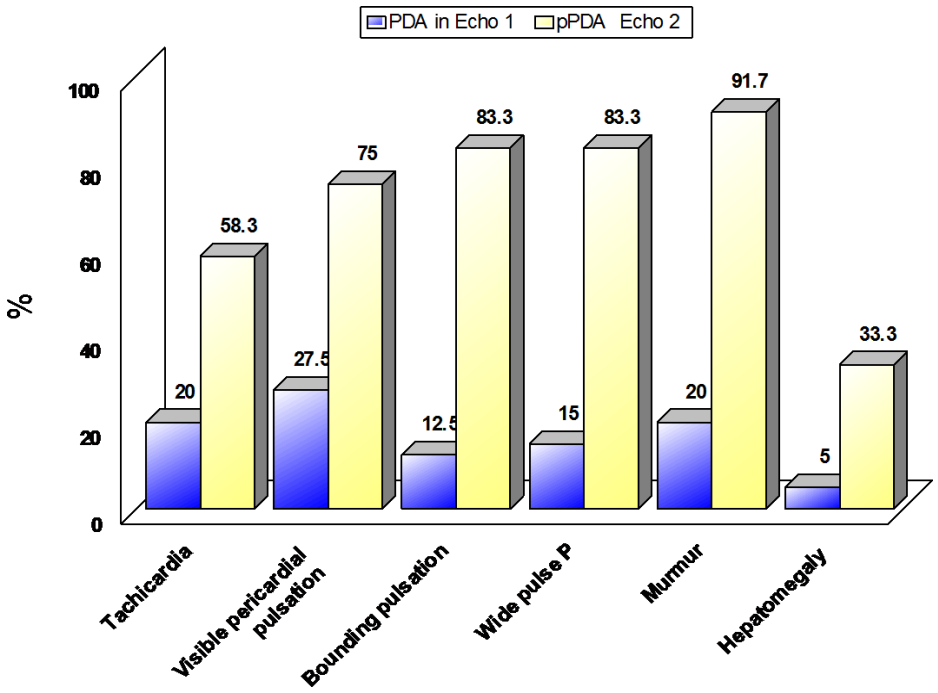

Figure 10: *Comparison between pertinent clinical sings in cases with PDA in Echo 1 vs. those with pPDA in Echo 2.*

Table 8: *Comparison between Echo 1 findings in PDA cases with tachycardia versus those without tachycardia.*

Echo finding in Echo 1	Tachycardia "n=8"	No tachycardia "n=32"	T-test P
Ductal diameter (in cm)			
Range	0.25-0.42	0.13-0.38	0.042*
Mean	0.35	0.22	
S.D.	0.089	0.089	
Maximal shunt velocity (cm/sec)			
Range	50-155	42-160	0.27
Mean	121.1	119.1	
S.D.	29.6	30.5	
Left atrium to aortic root ratio			
Range	1.3-1.6	1-1.45	0.046*
Mean	1.41	1.21	
S.D.	0.09	0.15	
P* is significant if< 0.05			

Table 9: *Comparison between Echo 1 findings in PDA cases with versus those without visible pericordial activity.*

Echo finding in Echo 1	Visible pericordial activity "n=11"	No visible pericordial activity "n=29"	T-test P
Ductal diameter (cm)			
Range	0.17-0.42	0.13-0.37	0.042*
Mean	0.32	0.21	
S.D.	0.19	0.08	
Maximal shunt velocity (cm/sec)			
Range	90-160	42-135	0.021*
Mean	135.9	100.3	
S.D.	31.2	41.3	
Left atrium to aortic root ratio			
Range	1.2-1.6	1-1.4	0.041*
Mean	1.42	1.21	
S.D.	0.16	0.33	
P* is significant if< 0.05			

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Table 10: *Comparison between Echo 1 findings in PDA cases with versus those without bounding pulsations.*

Echo finding in Echo 1	Bounding pulsations "n=5"	No bounding pulsations "n=35"	t-test P
Ductal diameter (cm)			
Range	0.25-0.42	0.13-0.38	0.047*
Mean	0.33	0.23	
S.D.	0.08	0.093	
Maximal shunt velocity(cm/sec)			
Range	55-160	42-150	0.21
Mean	122.3	118.9	
S.D.	35.2	34.6	
Left atrium to aortic root ratio			
Range	1.1-1.6	1-1.5	0.24
Mean	1.41	1.29	
S.D.	0.16	0.21	
P* is significant if< 0.05			

Table 11: *Echocardiographic Findings Based on Presence of Wide Pulse Pressure.*

Echo finding in Echo 1	Wide pulse pressure "n=6"	No wide pulse pressure "n=34"	T-test P
Ductal diameter (cm)			
Range	0.23-0.42	0.13-0.4	0.042*
Mean	0.32	0.24	
S.D.	0.05	0.09	
Maximal shunt Velocity(cm/sec)			
Range	60-160	42-150	0.23
Mean	120.3	119.8	
S.D.	33.5	31.2	
left atrium to aortic root ratio			
Range	1.2-1.6	1-1.4	0.12
Mean	1.31	1.28	
S.D.	0.22	0.106	
P* is significant if< 0.05			

Table 12: *Comparison between Echo 1 findings in PDA cases with versus those without murmur.*

Echo finding in Echo 1	Murmur "n=8"	No murmur "n=32"	T-test P
Ductal diameter (cm)			
Range	0.13-0.42	0.15-0.41	0.25
Mean	0.29	0.28	
S.D.	0.087	0.098	
Maximal shunt velocity(cm/sec)			
Range	85-160	42-135	0.041*
Mean	131.65	123.5	
S.D.	35.6	37.2	
Left atrium to aortic root ratio			
Range	1.1-1.6	1-1.4	0.16
Mean	1.37	1.28	
S.D.	0.19	0.11	
P* is significant if< 0.05			

Table 13: *Comparison between Echo 1 findings in cases with closed PDA and cases with pPDA in Echo 2.*

	Echo 1 findings in cases with closed PDA in Echo 2 "n = 28"	Echo 1 findings in cases with pPDA in Echo 2 "n = 12"	T-test P
Ductal diameter (cm)			
Range	0.13-0.3	0.17-0.42	0.046*
Mean	0.219	0.32	
S.D.	0.052	0.095	
Maximal shunt velocity (cm/sec)			
Range	42-140	50-160	0.023*
Mean	96.87	120.083	
S.D.	24.145	33.795	
Left atrium to aortic root ratio			
Range	1.1-1.4	1-1.6	0.176
Mean	1.247	1.3	
S.D.	0.091	0.181	
P* is significant if< 0.05			

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Table 14: *Comparison between Echocardiographic finding in Echo 1, 2 and 3.*

	Echo 1	Echo 2	Echo3
Echo findings in cases with patent duct			
Ductal diameter (cm)			
Range	0.13-0.42	0.11-0.45	0.21-0.42
Mean	0.235	0.296	0.315
S.D.	0.071	0.11	0.093
F, p		8.25, 0.023*	
Maximal shunt velocity (cm/sec)			
Range	42-160	90-160	114-150
Mean	104.013	134	135
S.D.	29.108	21.252	12.275
F, p		12.65, 0.0041*	
Left atrium to aortic root ratio			
Range	1-1.6	1.1-1.6	1.4-1.6
Mean	1.263	1.317	1.45
S.D.	0.125	0.164	0.1
F, p		2.09, 0.42	

(Table 14) compared echocardiographic findings in Echo1, Echo 2 and Echo 3 in cases with PDA. Duct diameter and maximal shunt velocity were significantly higher in Echo 3.

Discussion

Survival of the preterm neonates has increased significantly in the past two decades. This has resulted in the recognition of medical problems specific to these neonates that might contribute to increase in morbidity and mortality. One of these entities has been the occurrence of PDA. However, it remains unclear to what extent these complications occur by association, for example, because of prematurity, rather than the result of having a persistent PDA. Nonetheless, some have recommended the aggressive closure of the PDA in preterm neonates in the hope of preventing the associated morbidities, in particular CLD and poor growth. It is unclear, however, what proportion of preterm neonates have the potential to undergo spontaneous DA closure and when after birth this occurs or what number remain asymptomatic [112,113]. Knowledge of this and the variables that place these neonates at risk for persistent PDA may provide important insights into these issues and, importantly, permit a more selective approach to the study and treatment of persistent PDA.

The behavior of PDA in preterm newborn has been the subject of innumerable studies for almost 30 years. There are, however, few in the published literatures that have prospectively assessed the behavior of PDA in PT-NB, correlating clinical data with findings from echocardiography [114,115].

In this study we reviewed the behavior of PDA in 61 PT-NB admitted at the Neonatal Intensive Care Unit, Alexandria University Children's Hospital. Their gestational age ranged between 27 and 36 weeks. Twenty eight were males (45.9%) and 33 were females (54.1%). All neonates had respiratory distress of variable etiologies, 17 had TTN, 22 had neonatal pneumonia, and 22 had RDS. At the beginning of our study we decided to classify the neonates into 3 groups according to birth weight, group A (> 2kg), group B (1≤2kg) and group C (< 1 kg). This was only for simplification, however after going ahead through the work we find it is more suitable to join all cases and study the behavior the ductus in them.

Regarding the use of prostaglandin inhibitors in the different groups, 7 cases (all in group C) received prophylactic indomethacin (11.5%). Seventeen cases in all groups received therapeutic indomethacin (27.9%) and 2 cases (all in group B) received therapeutic oral ibuprofen (3.3%).

We observed 65% incidence of PDA on the third day of life, this incidence was significantly higher in group C (77.8%), and less in group A (53%) which is related to birth weight and gestational age (the more the gestational age and the birth weight , the less the occurrence of PDA) . This incidence decreased to 19.6% on the 2nd week and to only 8.1% on the 3rd week. This decrease in incidence ofcourse related to maturity and intervention by prostaglandin inhibitors therapy.

Reller et al (7) reported an incidence of PDA on the third day of postnatal life, of around 50% of NB with GA at birth of less than 29 weeks, and an even higher incidence among those with hyaline membrane disease (77%).

Afiune et al, [116] had studied 61 NB in Brazil with gestational age less than 34 weeks, and reported 34.4% incidence of PDA on the third day of life. This incidence was significantly higher among NB with birth weights below 1,000 g (58.8%) and also among those with GA at birth of less than 30 weeks (52.2%).

Koch et al, (113) study in USA included 122 neonates with birth weight less than 1 kg. They found that 80% of cases have PDA on the second day of life and 66% have PDA on the fourth day of life.

It may be beneficial to predict which preterm neonates are likely to spontaneously close their DA permanently and those at risk for pPDA. This would permit the design of studies to determine the actual impact of pPDA with a significant left-to-right shunt on neonatal morbidity (e.g. CLD), mortality and to establish appropriate treatment regimens to close the DA in neonates at risk for complications of extreme prematurity.

In our study there is inverse relationship between BW and EGA, and the occurrence of PDA. This is in agreement with Furzan et al and Mouzinho et al studies results. In contrast Koch et al, (113) study included only ELBW and excluded neonates more than 1000 g BW, they found no relationship between BW and PDA, however there was a very significant increase in permanent DA closure as EGA advanced and a more than three fold increase in the rate of PDA as EGA decreased [117,118].

In our work we tried to study the effect of some maternal risk factors (Caesarean section delivery, preterm labour pain, pre-eclampsia, diabetes, PROM, antepartum hge, antenatal corticosteroids, UTI, twin pregnancy, and positive consanguinity) on ductus arteriosus. None of these risk factors has been proved to affect early closure of DA.

Koch et al, (113) found no effect of ethnicity, maternal hypertension, antenatal steroids and cesarean delivery on early closure of PDA, which is in agreement with our study. In contrast, Morales et al, [119] reported that antenatal steroids decrease the sensitivity of the DA to prostaglandin E2 and to reduce the occurrence of pPDA. In our study antenatal steroids didn't affect DA closure significantly, which may be related to the smaller number of cases that received antenatal corticosteroid as a result of the neglected antenatal care.

Clinically stable neonates who do not require oxygen or ventilatory therapy generally do not have a PDA that is haemodynamically significant, and they do well even without treatment [120].

Among neonates with PDA we found that 6 neonates (15%) diagnosed as TTN, 16 neonates (40%) diagnosed as neonatal pneumonia and 18 neonates (45%) diagnosed as RDS. While in neonates with early ductal closure there were 11(52.8%) diagnosed as TTN, 6(28.6%) as neonatal pneumonia and 4(19%) as RDS. The differences in-between were statistically significant, so the more severe the neonatal respiratory problem, the more likelihood of PDA. We found also that the more the oxygen requirement of the baby the more likelihood of PDA. In cases with PDA, 9 cases were on head box (22.5%), 10 cases were on CPAP (25%) and 21 cases were on IPPV (52.5%). Among cases with early closure, 13 cases were on head box (61.9%), 5 cases were on CPAP (23.8%) and 3 cases (14.3%) were on IPPV.

Koch et al, (113) found that in cases with spontaneous closure of the DA, 22 neonates were diagnosed as RDS (52%) and in cases with PDA 63 neonates were diagnosed as RDS (79%). The higher incidence of RDS in this study is related to inclusion of cases less than 1000g only where RDS is more common than other diagnoses. In agreement to the previous results, Siassi et al, [121] study in USA included 150 low birth weight newborns. Forty two cases had PDA, 32 (67%) of them had respiratory distress (12 required IPPV). One hundred and eight didn't have PDA, 27 (25%) had respiratory distress (only 4 required IPPV).

Reliance on clinical signs, such as an active pericordium, tachycardia, bounding pulses, wide pulse pressure, or a murmur will usually make the diagnosis of a PDA but only after the left to right shunt through the duct has been significant for some days. Blinded comparison of these clinical signs to echocardiographic criteria of ducal haemodynamic significance, have shown that it is normal for haemodynamically significant ducts to be clinically silent for the first 2 to 3 days of life. From day 4 onwards, physical signs, particularly the murmur, become more sensitive but some inaccuracy persists up to day 7 of life. Therefore, accurate and early diagnosis of significant ductal shunting depends on echocardiography [122].

In our study we compared pertinent cardiac signs of PDA in cases diagnosed with Echo 1 (done on the third day of life) versus those with pPDA in echo 2 (done on the 2nd week of life). Forty cases were proved to have PDA in Echo 1, 8 (20%) cases had tachycardia, 11 (27.5%) had visible pericordial pulsations, 5 (12.5%) had bounding pulsations, 6 (15%) had wide pulse pressure, 8 (20%) had murmur and 2(5%) had hepatomegaly. On the other hand 12 cases had proved to have pPDA in Echo 2, 7 (58.3%) cases had tachycardia, 9 (75%) had visible pericardial activity, 10 (83.3%) had bounding pulsations and wide pulse pressure, 11(91.7%) had murmur and 4 (33.3%) had hepatomegaly. All were statistically significant, so we can't relay on clinical sings to diagnose PDA in the first few days of life but they become more reliable after these few days.

Now we will try to explain the absence of clinical sings of PDA in the first few days of life in cases proved to have PDA by echocardiography. Regarding tachycardia in preterm newborn with a big left-to-right ductal shunt, the preload is greatly increased due to increased pulmonary venous return, and afterload is greatly reduced; blood leaving the left ventricle pours into the low resistance pulmonary circulation via the ductus. In serial studies of preterm infants during therapeutic ductal closure, there was barely a discernible difference between heart rates. The left ventricular stroke volume, on the other hand, fell by over half. The increased left ventricular output due to the ductal shunt is in fact achieved by an increase in stroke volume, not heart rate. Many other studies have shown this phenomenon; LV stroke volume cans double or even triple with a large shunt and a healthy myocardium [123]. In summary, change in cardiac output in response to changing ductal shunting is mostly mediated by a change in stroke volume, not heart rate. Since we also know that tachycardia is also a feature of hypovolaemia, stress of various types, and most inotropic drugs, it is safe to conclude that changes in heart rate do not reliably reflect changes in left-to-right ductal shunting.

Regarding bounding pulsation, it is caused by a wide pulse pressure, i.e. a big difference between the systolic and diastolic aortic pressure. In a large infant with a PDA the systolic pressure is maintained whilst diastolic aortic pressure is reduced. However, ventilated preterm infants are less able to maintain the systolic pressure with a large left-to-right ductal shunt. Both diastolic and systolic pressure is reduced due to failure of the left ventricle to adequately elevate LV stroke volume and thus the pulse pressure remains unchanged. Systolic pressure only returns to normal after ductal closure,

and diastolic pressure rises with it. Hence, wide pulse pressure is not a reliable sign of a left-to-right ductal shunt in very low-birth weight infants.

It needs to be remembered that a systolic murmur can arise from a number of different causes. It may be dangerous to assume it comes from a ductus. There may be congenital heart disease such as pulmonary or aortic stenosis for example, or an outflow murmur from cardiac hypertrophy secondary to maternal diabetes or steroid therapy. Following indomethacin or Ibuprofen a systolic heart murmur may persist leading to the presumption that the duct remains patent. Careful examination may reveal that the murmur goes through to the back more than before, and that the chest radiograph seems to show less pulmonary plethora. This is classical of branch pulmonary artery stenosis readily detected on echocardiography and a common physiological occurrence in the preterm after ductal closure a further course of indomethacin is not indicated [124]. A pansystolic murmur may be uncommonly be due to mitral regurgitation, which is usually a transient functional phenomenon related to myocardial dysfunction before and/or after ductal closure. In summary, a murmur is a late sign of a large left-to-right ductal shunt and although relatively specific, may represent pathology other than a patent ductus (32).

A hyperactive pericordium and a mid-diastolic flow murmur (from increased flow across the mitral valve) are typical with any large left-to-right shunt. Tuning in to a mid-diastolic murmur with a stethoscope at heart rates of over 160 beats per min in a noisy incubator can be very difficult, but pericordial hyperactivity is easily seen. There are many other things which can cause the pericordium to be hyperactive-particularly sepsis, CO2 retention (through vasodilatation) and inotropes and vasodilators. It is hyperactive because there is an increased stroke volume. Since the pericordium is not always overactive with a large ductal shunt in the preterm one might guess it is because the cardiac output is not so elevated. Perhaps these physical signs, like the murmur, tend to occur with a ductus when there is a healthy myocardial response to the increased demand for blood flow, with high cardiac output, and tend to be absent when there is an element of myocardial failure. Despite these problems, a hyperactive pericordium is one of the more specific, though not sensitive, signs of a large left-to-right ductal shunt when present.

Regarding hepatomegaly, the size of the liver is difficult to assess accurately in a tiny preterm neonate and may be pushed down from positive pressure ventilation. However, the true size of the liver reflects both right atrial pressure and the state of hydration. Fluid restriction not only reduces left atrial size on echocardiography, but also reduces the size of the liver, and body weight in general. The duct can be huge, but if blood volume is depleted enough, the left and right atrial pressure will be low, and the liver will be small. True hepatomegaly is difficult to assess but can be a useful sign of left or right cardiac failure and fluid overload. However, its absence does not indicate absence of a large left-to-right ductal shunt.

Skelton et al, (122) found that clinical signs were poor at detecting a significant PDA in the first 4 days of life. On day 1, none of the 10 infants with a significant PDA had a murmur. By day 4, clinical signs were better at detecting a significant PDA, but specificity remained poor with many false positive signs. Six infants had murmurs with a closed duct. The development of echocardiographic haemodynamic significance preceded the development of physical signs by a mean of 1.8 days. Significant ductal shunts often occurred silently, but the development of a murmur often marked an increase in the velocity of the flow through the duct rather than an increase in the size of a shunt. This study confirms that echocardiography is required for the reliable early diagnosis of a PDA in ventilated preterm infants.

In agreement with our results Alagarsamy et al, found 12 neonates Out of 25 preterm newborns included in this study, had haemodynamically significant PDA with left-to-right shunt. Two infants had small PDA and in 11 infants the ductus arteriosus was not patent. PDA infants had lower gestational age and birth weight Systolic and mean blood pressures were lower in the PDA group. A poor association between heart murmur, hyperdynamic chest and dorsalis pedis pulse, and the presence of PDA was revealed, concluding that Echocardiogram is required for early diagnosis of PDA in preterm infants, as clinical signs are not reliable in the first few days of life [125].

Davis et al, (48) found that in the twenty-three infants who had a PDA with left-to-right shunting, the precision of clinical signs was modest, (15%) for the bounding pulsations, (32%) for active pericordium, and (41%) for murmur. Therefore echocardiography is required to confirm or refute a diagnosis of PDA.

Afiune et al, (116) had performed the clinical assessment of newborn infants with PDA detected by echocardiographic examination on the third day of life. They detected heart murmur in eleven NB (18.0%), visibly increased pericordial activity in 8 (13.1%) and increased pulse pressure in just 2 NB (3.3%).

Siassi et al, (121) found that in cases with PDA, heart murmur was present in 18 (42%) infants by the 4th day of life and in 38 (90.4%) infants by 7 days. the higher incidence of heart murmur in this study may be related to the evaluation on the 4th day of life, while in our study evaluation has been done on the 3rd day. Also they didn't evaluate other pertinent clinical signs.

The X-ray findings couldn't be compared as pulmonary congestion was a common finding in these cases and couldn't be related to PDA only, but also to the cause of respiratory distress. Also in cases with severe respiratory distress the primary lung pathology usually hinders the picture of pulmonary congestion. Cardiomegaly was present in 2 cases only.

We also tried to compare echocardiographic findings in PDA cases (proved by Echo 1) that had pertinent clinical signs in the first 3 days of life vs. those hadn't these signs. In PDA cases with tachycardia the mean duct diameter was (0.35 cm), while in those without tachycardia the duct diameter was (0.22 cm), also the mean left atrium to aortic root ratio was (1.41) in cases with tachycardia and (1.21) in cases without

tachycardia, the differences were statistically significant. While the difference in the maximal shunt velocity wasn't. So PDA cases with tachycardia usually have larger duct diameter and left atrium to aortic root ratio.

The echocardiographic parameters in PDA cases with visible pericordial activity vs. those without visible pericordial activity were; for duct diameter (0.32 vs.0.21cm), maximum shunt velocity (135.9 vs. 100.3 cm/sec), and left atrium to aortic root ratio (1.42 vs. 1.21). This signifies the importance of early echocardiographic evaluation of neonates with visible pericordial activity.

The duct diameter was significantly higher in PDA cases with bounding pulsations (0.33 vs. 0.23 cm) and also in those with wide pulse pressure (0.32 vs. 0.24 cm), no significant differences as regard maximal shunt velocity and left atrium to aortic root ratio were found between cases with bounding pulsations or wide pulse pressure and those without these signs.

The maximum shunt velocity was significantly greater in PDA cases with murmur vs. those without murmur (131.6 vs. 123.5). No significant differences were found in duct diameter and left atrium to aortic root ratio between cases with and without murmur.

Roberson et al, (114) studied the relation between echocardiographic and clinical findings in cases with PDA. The echocardiographic parameters in their study were duct diameter, left atrium to aortic root ratio , color Doppler flow map area of the duct jet, color Doppler flow map length of duct jet and color Doppler flow map width of duct jet. The clinical signs were visible pericordial activity, murmur, wide pulse pressure and bounding pulsations. In agreement with our study, they found that all echocardiographic parameters were greater in PDA cases with visible pericordial activity vs. those without visible pericordial activity. The color Doppler flow map area of the duct jet was greater in cases with murmur vs. those without murmur. In contrast to our study no differences in any of the echocardiographic parameters were found between PDA cases with vs. those without bounding pulsations or wide pulse pressure. This may be related to the advances in echocardiographic devices and technology that can more precisely measure the different duct parameters.

Skinner et al, compared Doppler echocardiograms from preterm infants with a large shunt and a murmur (n=55), to those with a large shunt and no murmur (n=62), the two groups had similar left atrial dimensions. The main difference was that those infants with a murmur tended to have a higher left ventricular output (mean 501 vs. 352 ml/kg/min) and higher left ventricular stroke volume (3.3 vs. 2.3 ml/kg). The pattern of flow through the duct was typically highest in late systole and very low in late diastole.

In our study 28 (70%) of the 40 NB with PDA on the third day of life had exhibited ductus arteriosus closure in Echo 2 and in 12 NB (30%) this closure did not take place . these two groups were compared regarding Echo 1 findings. In cases with closed PDA in Echo 2 the duct diameter in Echo 1 ranged from 0.13 to 0.3 cm with mean duct diameter 0.219 cm, the maximal shunt velocity ranged from 42 to 150 m/sec with mean of 96.87 m/sec and the left atrium to aortic root ratio ranged from 1.1 to 1.4 with a mean of 1.24. While in the group with pPDA in Echo 2 the duct diameter in Echo 1 ranged from 0.17 to 0.42 with mean of 0.320 cm, the maximal shunt velocity ranged from 50 to 160 m/sec with mean of 120.08 m/sec and the left atrium to aortic root ratio ranged from 1.1to 1.4 with a mean of 1.3, the difference in ductal diameter and the maximal shunt velocity was statistically significant while the difference in the left atrium to aortic root ratio was not. So we can conclude that the more the duct diameter and the maximal shunt velocity, the less likely the closure of PDA.

One measurement that has always been much used in the literature to assess the ductus arteriosus is the left atrium/aorta ratio, with a ratio of more than 1.5 exhibiting high sensitivity and specificity for detecting it, as reported by Iyer & Evans.

In this study, however, we did not observe any effect of PDA on this echocardiographic measurement, with no significant difference demonstrated. This might be because in many PT-NB, the size of the aorta is already enlarged and, even if the left atrium also increases, the LA/AO ratio may not. Another motive may be the presence of a patent foramen ovale, which may reduce the size of the left atrium, by left to right interatrial shunting, even in the presence of a large ductus arteriosus.

In Afiune et al study, (116) follow up of 21 neonates with PDA on the third day of life was done. Spontaneous closure of the ductus was observed during follow-up of 7 neonates (Group A, 33%), in contrast with p PDA in 14 neonates (Group B, 67%). The larger percent of closed cases in the follow up in our study may be related to therapeutic intervention in some cases. Afiune found that Group B had a larger ductus diameter in relation to Group A (2.6±0.6 mm vs. 1.4±0.6 mm; p = 0.003). The smaller mean ductal diameter in this study may be related to the smaller gestational age (mean 30). In agreement to our results, there was no statistical difference between the 2 groups regarding left atrium to aortic root ratio.

Kluckow et al, (51) had performed a study to identify early echocardiographic markers allowing prediction of subsequent symptomatic patent ductus arteriosus (PDA).One hundred sixteen preterm infants (< 1500 gm) requiring mechanical ventilation underwent echocardiography at a mean postnatal age of 19 hours (range, 7 to 31 hours). Three potential markers were studied: the left atrial to aortic root ratio, pulsed Doppler signal within the course of the duct (ductal diameter), and the direction of postductal aortic diastolic flow. Subsequent ductal closure or significant patency (if suspected clinically) was confirmed echocardiographically. They found that significant PDA developed in 42 infants (36%). Ductal diameter was the most accurate echocardiographic marker in predicting subsequent PDA.

In our study we compared echocardiographic findings in Echo 1, 2 and 3. It showed that in Echo 1 duct diameter ranged from 0.13 to 0.42 with mean of 0.235 cm, maximal shunt velocity ranged from 42 t0 160 m/sec with mean of 104 m/sec and the left atrium to aortic root ratio ranged from 1 to 1.6 with mean of 1.26. In Echo 2 the duct diameter ranged from 0, 11 to 0.45

cm with mean of 0.29, the maximal shunt velocity ranged from 90 to 160 m/sec with mean of 134 m/sec and the left atrium to aortic root ratio ranged from 1.1 to 1.6 with mean of 1.31. Lastly in Echo 3 the duct diameter ranged from 0, 21 to 0.42 cm with mean of 0.315, the maximal shunt velocity ranged from 114 to 150 m/sec with mean of 135 m/sec and the left atrium to aortic root ratio ranged from 1.4 to 1.6 with mean of 1.45. The differences in the duct diameter and in the maximal shunt velocity were statistically significant. Concluding that cases with persistent PDA more than 3 weeks, usually have larger ductal diameter and maximal shunt velocity, and will usually persist later on [126].

Summary

The present study was conducted on 61 preterm neonates (28 males and 33 females) admitted at NICU, Alexandria University Children's Hospital. Seventeen were more than 2 kg, 26 were 1-2 kg and 18 were less than 1 kg. The gestational age of the studied groups ranged from 27 to 36 wks.

All neonates included in the study were subjected to:

1. Full history taking including antenatal and perinatal history.
2. Clinical examination stressing on the cardiovascular system especially pertinent signs of PDA (tachycardia, visible pericordial activity, murmur, bounding pulsation and/or wide pulse pressure. It was done initially in the first three days of life and repeated daily in the first week.
3. Chest x ray.
4. Monitoring oxygen saturation by pulse oximetry.
5. Echocardiography done on the third day of life (Echo 1) repeated in cases with PDA on the second week (Echo2) and on the third week (Echo 3).

Such evaluation aimed to detect the following data:

1. Patency of the duct.
2. Internal ductal diameter.
3. Maximal shunt velocity.
4. Ratio of the diameter of the left atrium to the aortic root.

The incidence of PDA was 65% in Echo 1, 19.6% in Echo 2 and 8.1% in Echo 3. There is inverse relationship between BW and EGA, and the occurrence of PDA. The results of comparing cases with PDA vs. cases with early spontaneous duct closure regarding some maternal risk factors were statistically insignificant.

Comparing neonates with early duct closure vs. those with in PDA in Echo 1, regarding the cause of respiratory distress showed that early ductal closure was significantly higher among TTN cases, while ductal patency was significantly higher among RDS and pneumonia cases. Comparing the previous two groups regarding the method of oxygenation showed that early ductal closure was significantly higher among neonates on head box, while ductal patency was significantly higher among neonates on IPPV. So the more the respiratory problem and the oxygen requirement, the more the likelihood of PDA.

Comparison pertinent Clinical sings of PDA between neonates with PDA in Echo 1 vs. those with pPDA in Echo 2 .Forty cases were proved to have PDA in Echo 1, 8 (20%) cases had tachycardia, 11 (27.5%) had visible pericordial pulsations, 5 (12.5%) had bounding pulsations, 6 (15%) had wide pulse pressure, 8 (20%) had murmur and 2(5%) had hepatomegaly. On the other hand 12 cases had proved to have pPDA in Echo 2, 7 (58.3%) cases had tachycardia, 9 (75%) had visible pericardial activity, 10 (83.3%) had bounding pulsations and wide pulse pressure, 11(91.7%) had murmur and 4 (33.3%) had hepatomegaly. All were statistically significant, so we can't relay on clinical sings to diagnose PDA in the first few days of life but they become more reliable after these few days.

Comparing echocardiographic findings in PDA cases (proved by Echo 1) that had pertinent clinical signs in the first 3 days of life vs. those hadn't these signs. In PDA cases with tachycardia the mean duct diameter was (0.35 cm), vs. (0.22 cm) in those without tachycardia, also the mean left atrium to aortic root ratio was (1.41) in cases with tachycardia and (1.21) in cases without tachycardia. These differences were statistically significant, while the difference in the maximal shunt velocity wasn't. So PDA cases with tachycardia usually have larger duct diameter and left atrium to aortic root ratio.

The echocardiographic parameters in PDA cases with visible pericordial activity vs. those without visible pericordial activity were; for duct diameter (0.32 vs.0.21 cm), maximum shunt velocity (135.9 vs. 100.3 cm/sec), and left atrium to aortic root ratio (1.42 vs. 1.21). This signifies the importance of early echocardiographic evaluation of neonates with visible pericordial activity.

The duct diameter was significantly higher in PDA cases with bounding pulsations (0.33 vs. 0.23 cm) and also in those with wide pulse pressure (0.32 vs. 0.24 cm), no significant differences as regard maximal shunt velocity and left atrium to aortic root ratio were found between cases with bounding pulsations or wide pulse pressure and those without these signs.

The maximum shunt velocity was significantly greater in PDA cases with murmur vs. those without murmur (131.6 vs. 123.5). No significant differences were found in duct diameter and left atrium to aortic root ratio between cases with and without murmur.

Retrograde comparison between cases with closed PDA vs. cases with pPDA regarding Echo 1 findings, showed that the difference in ductal diameter (0.219 vs. 0.32 cm) and the maximal shunt velocity (96.87 vs. 120.08 m/sec) was statistically significant, while the difference in the left atrium to aortic root ratio was not. So the more the duct diameter and the maximal shunt velocity, the less likely the closure of PDA.

Comparing Echo 1, 2 and 3 findings showed that cases with persistent PDA more than 3 weeks, usually have larger ductal diameter and maximal shunt velocity, and will usually persist later on.

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Conclusions

1. Prevention of prematurity is the main way to decrease the incidence of PDA.
2. The more the degree of respiratory distress in the preterm neonates, the more likely the patency of the ductus arteriosus.
3. Clinical sings of PDA are neither reliable nor accurate in the first 3 days of life and become more reliable after theses early days for PDA diagnosis.
4. Echocardiography is essential tool for early and accurate diagnosis of PDA.
5. Some clinical signs can be correlated to some echocardiographic parameters; presence of these signs signifies early confirmation of PDA by Echocardiography.
6. Some Echocardiography parameters can be used as prognostic in the management of PDA e.g. the duct diameter and the maximal shunt velocity (the more the duct diameter and the maximal shunt velocity, the more likely the persistent of DA).
7. Cases with persistent PDA more than 3 weeks, usually have larger ductal diameter and maximal shunt velocity, and will not usually close spontaneously.
8. It is advisable to the neonatologist to learn how to do echocardiographic screening for PDA in the early days of life.

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References

1. Rudolph AM. The ductus arteriosus and persistent patency od the ductus arteriosus. CHD. 2001:155-96.
2. Miyague NI. Preterm neonates with patent ductus arteriosus. J Pediatr. 2005;81:429-30.
3. Bergwerff M, DeRuiter MC, Gittenberger-de Groot AC. Comparative anatomy and ontogeny of the ductus arteriosus, a vascular outsider. Anat Embryol (Berl). 1999;200:559-71.
4. Rudolph AM. The fetal circulation and postnatal adaptation. Congenital diseases of the heart: clinical-physiological considerations. 2001;2:3-44.
5. Rudolph AM. The development of concepts of the ontogeny of the pulmonary circulation. PFC. 2000.
6. Van Overmeire B, Chemtob S. The pharmacology closure of the patent ductus arteriosus. Seminars in Fetal & Neonatal Medicine. 2005;10:177-84.
7. Reller MD, Rice MJ, McDonald RW. Review of studies evaluating ductal patency in the premature infant. J Pediatr. 1993;122: 59-62.
8. Evans N, Malcolm G, Osborn D, et al. Diagnosis of patent ductus arteriosus in preterm infants. Adv Neonatal Care. 2004;5(3):86-97.
9. Lucas VW, Ginsberg HC. Cardiovascular aspects. In: Goldsmith JP, Kanotkin AH eds. Assisted Ventilation of the Neonate. 4 ed: Saunders; 2000; 423-27.
10. Smith GC. The pharmacology of the ductus arteriosus. Pharmacol. 1998;50(1):35-58.
11. Sharpe GL, Larsson KS. Studies on closure of the ductus arteriosus. X. In vivo effect of prostaglandin. Prostaglandins. 1975;9(5):703-19.
12. Coceani F, Liu YA, Seidlitz E, et al. Endothelin A receptor is necessary for O2 constriction but not closure of ductus arteriosus. Am J Physiol. 1999;277(4):1521-31.
13. RA C. International Union of Pharmacology classification of prostanoid receptors: properties, distribution and structure of the receptors and their subtypes. Pharmacol Rev. 1994;46:205-29.
14. Slomp J, Van Munsteren JC, Poelmann RE. Formation of intimal cushions in the ductus arteriosus as a model for vascular intimal thickening. An immunohistochemical study of changes in extracellular matrix components. Atherosclerosis. 1992;93(1-2):25-39.
15. Thorburn GD. The placenta, PGE2 and parturition. Early Hum Dev. 1992;29(1-3):63-73.
16. Seidner SR, Chen YQ, Oprysko PR, et al. Combined prostaglandin and nitric oxide inhibition produces anatomic remodeling and closure of the ductus arteriosus in the premature newborn baboon. Pediatr Res. 2001;50(3):365-73.
17. Moncada S, Higgs A, Furchgott R. XIV. International union of pharmacology nomenclature in nitric oxide research. Pharmacol Rev. 1997;49(2):137-42.
18. Wang R, Wu L. The chemical modification of KCa channels by carbon monoxide in vascular smooth muscle cells. J Biol Chem. 1997;272(13):8222-6.
19. Evans N, Henderson-Smart D. Cardiorespiratory adaptation to extrauterine life. Fetal medicine: basic science and clinical practice.—Churchill Livingstone. 1999:1045-52.

Citation: *Taha A. S. Clinical and echocardiographic study of the ductus arteriosus in preterm infants. J Preg Neonatal Med. 2024;8(5):221*

20. Bodach E, Coceani F, Dumbrille A, et al. The response of the isolated ductus arteriosus to transmural stimulation and drugs. Br J Pharmacol. 1980;71(2):419.

21. Smith GC, McGrath JC. Prostaglandin E2 and fetal oxygen tension synergistically inhibit response of isolated fetal rabbit ductus arteriosus to norepinephrine. J Cardiovasc Pharmacol. 1991;17(6):861-6.

22. Kriska M, Smiesko V, Cerletti C, et al. Interaction of prostaglandins and the myogenic factor in the mechanism of closure of the ductus arteriosus. Physiol Bohemoslov. 1990;39(3):207-16.

23. Tada T, Wakabayashi T, Nakao Y, et al. Human ductus arteriosus: A histological study on the relation between ductal maturation and gestational age. Acta Pathol Jpn. 1985;35(1):23-34.

24. Dudell GG, Gersony WM. Patent ductus arteriosus in neonates with severe respiratory disease. J Pediatr. 1984;104(6):915-20.

25. Hammerman C, Strates E, Valaitis S. The silent ductus: its precursors and its aftermath. Pediatric cardiology. 1986;7:121-7.

26. Rudolph AM, Mayer FE, Nadas AS, et al. Patent ductus arteriosus: A clinical and hemodynamic study of 23 patients in the first year of life. Pediatrics. 1958;22(5):892-904.

27. Moore P, Michael M, Patent Ductus Arteriosus, et al. In: Hugh D, David J, Robert E eds. Moss and Adams' Heart Disease in Infants, Children, and Adolescents: Including the Fetus and Young Adults. Lippincott Williams & Wilkins 2008; 33:684-93.

28. Baylen BG, Ogata H, Oguchi K, et al. The contractility and performance of the preterm left ventricle before and after early patent ductus arteriosus occlusion in surfactant-treated lambs. Pediatric research. 1985;19(10):1053-8.

29. Lebowitz EA, Novick JS, Rudolph AM. Development of myocardial sympathetic innervation in the fetal lamb. Pediatr Res. 1972;6(12):887-93.

30. Hoffman JI, Buckberg GD. Regional myocardial ischemia—causes, prediction and prevention. Vascular Surgery. 1974 Mar;8(2):115-31.

31. Delivoria-Papadopoulos M, Roncevic NP, Oski FA. Postnatal changes in oxygen transport of term, premature, and sick infants: the role of red cell 2, 3-diphosphoglycerate and adult hemoglobin. Pediatric research. 1971;5(6):235-45.

32. Skinner J. Diagnosis of patent ductus arteriosus. J. Clin. Neonatol. 2001;6(10):49-61.

33. McNamara PJ, Sehgal A. Towards rational management of the patent ductus arteriosus: the need for disease staging. Archives of Disease in Childhood-Fetal and Neonatal Edition. 2007 Nov 1;92(6):F424-7.

34. Urquhart DS, Nicholl RM. How good is clinical examination at detecting a significant patent ductus arteriosus in the preterm neonate?. Arch Dis Child. 2003;88(1):85-6.

35. Ekici F, Atasay B, Günlemez A, et al. Management of patent ductus arteriosus in preterm infants. Anadolu Kardiyol Derg. 2006;6(1):28-33.

36. Morley CJ, Morley R. Follow up of premature babies treated with artificial surfactant (ALEC). Archives of Disease in Childhood. 1990;65(7):667-9.

37. Clyman R. The role of the patent ductus arteriosus in respiratory distress syndrome. Semin Perinatol. 1984; 8(4).293-299.

38. Bancalari E. Changes in the pathogenesis and prevention of chronic lung disease of prematurity. American journal of perinatology. 2001;18(01):001-10.

39. D'Angio CT, Maniscalco WM. Bronchopulmonary dysplasia in preterm infants: pathophysiology and management strategies. Pediatric drugs. 2004;6:303-30.

40. Garland J, Buck R, Weinberg M. Pulmonary hemorrhage risk in infants with a clinically diagnosed patent ductus arteriosus: a retrospective cohort study. Pediatrics. 1994;94(5):719-23.

41. Coombs RC, Morgan M, Durbin GM, et al. Gut blood flow velocities in the newborn: effects of patent ductus arteriosus and parenteral indomethacin. Arch Dis Child. 1990;65(10):1067-71.

42. Wheatley CM, Dickinson JL, Mackey DA, et al. Retinopathy of prematurity: recent advances in our understanding. Br J Ophthalmol. 2002;86(6):696-700.

43. Evans N, Moorcraft J. Effect of patency of the ductus arteriosus on blood pressure in very preterm infants. Arch Dis Child. 1992;67(10):1169-73.

44. Shimada S, Kasai T, Konishi M, et al. Effects of patent ductus arteriosus on left ventricular output and organ blood flows in preterm infants with respiratory distress syndrome treated with surfactant. J Pediatr. 1994;125(2):270-7.

45. Limperopoulos C, Benson CB, Bassan H, et al. Cerebellar hemorrhage in the preterm infant: ultrasonographic findings and risk factors. Pediatrics. 2005;116(3):717-24.

46. Jim WT, Chiu NC, Chen MR, et al. Cerebral hemodynamic change and intraventricular hemorrhage in very low birth weight infants with patent ductus arteriosus. Ultrasound Med Biol. 2005;31(2):197-202.

47. Kääpä P, Seppänen M, Kero P, et al. Pulmonary hemodynamics after synthetic surfactant replacement in neonatal respiratory distress syndrome. J Pediatr. 1993;123(1):115-9.

48. Davis P, Turner-Gomes S, Cunningham K, et al. Precision and accuracy of clinical and radiological signs in premature infants at risk of patent ductus arteriosus. Arch Pediatr Adolesc Med. 1995;149(10):1136-41.

49. Evans N. Current controversies in the diagnosis and treatment of patent ductus arteriosus in preterm infants. Adv Neonatal Care. 2003;3(4):168-77.

Citation: *Taha A. S. Clinical and echocardiographic study of the ductus arteriosus in preterm infants. J Preg Neonatal Med. 2024;8(5):221*

50. Su BH, Peng CT, Tsai CH. Echocardiographic flow pattern of patent ductus arteriosus: a guide to indomethacin treatment in premature infants. Arch Dis Child Fetal Neonatal Ed. 1999;81(3):97-200.
51. Kluckow M, Evans N. Early echocardiographic prediction of symptomatic patent ductus arteriosus in preterm infants undergoing mechanical ventilation. J Pediatr. 1995;127(5):774-9.
52. Evans N. Diagnosis of patent ductus arteriosus in the preterm newborn. Arch Dis Child. 1993;68(1):58.
53. Su BH, Peng CT, Tsai CH. Echocardiographic flow pattern of patent ductus arteriosus: a guide to indomethacin treatment in premature infants. Arch Dis Child Fetal Neonatal Ed. 1999; 81:197-200.
54. Su BH, Watanabe T, Shimizu M, et al. Echocardiographic assessment of patent ductus arteriosus shunt flow pattern in premature infants. Arch Dis Child Fetal Neonatal Ed. 1997;77(1):36-40.
55. Choi BM, Lee KH, Eun BL, et al. Utility of rapid B-type natriuretic peptide assay for diagnosis of symptomatic patent ductus arteriosus in preterm infants. Pediatrics. 2005;115(3):255-61.
56. Schmidt B, Davis P, Moddemann D, et al. Long-term effects of indomethacin prophylaxis in extremely-low-birth-weight infants. N Engl J Med. 2001;344(26):1966-72.
57. Clyman RL. Recommendations for the postnatal use of indomethacin: an analysis of four separate treatment strategies. J Pediatr. 1996;128(5):601-7.
58. Edwards AD, Wyatt JS, Richardson C, et al. Effects of indomethacin on cerebral haemodynamics in very preterm infants. Lancet. 1990;335(8704):1491-5.
59. Fowlie PW. Intravenous indomethacin for preventing mortality and morbidity in very low birth weight infants. Cochrane Database Syst Rev. 2000;(2):CD000174-.
60. Van Overmeire B, Allegaert K, Casaer A, et al. Prophylactic ibuprofen in premature infants: a multicentre, randomised, double-blind, placebo-controlled trial. Lancet. 2004;364(9449):1945-9.
61. Gournay V, Roze JC, Kuster A, et al. Prophylactic ibuprofen versus placebo in very premature infants: a randomised, double-blind, placebo-controlled trial. Lancet. 2004;364(9449):1939-44.
62. Cooke L, Steer PA, Woodgate PG, Cochrane Neonatal Group. Indomethacin for asymptomatic patent ductus arteriosus in preterm infants. Cochrane Database Syst Rev. 1996;2010(1).
63. Fowlie PW. Managing the baby with a patent ductus arteriosus. More questions than answers?. Arch Dis Child Fetal Neonatal Ed. 2005;90(3):190-190.
64. Knight DB. The treatment of patent ductus arteriosus in preterm infants. A review and overview of randomized trials. Semin Neonatol. 2001; 699(1):63-73.
65. Bell EF, Warburton D, Stonestreet BS, et al. Effect of fluid administration on the development of symptomatic patent ductus arteriosus and congestive heart failure in premature infants. N Engl J Med. 1980;302(11):598-604.
66. Semama DS. Diuretics in preterm infants. Arch Pediatr. 2006;13(4):379-87.
67. Brion LP, Campbell D, Cochrane Neonatal Group. Furosemide for prevention of morbidity in indomethacin- treated infants with patent ductus arteriosus. CDSR. 1996;2010(1).
68. BG K. Cardiac glycosides & other drugs used in congestive heart failure Int J Basic Clin Pharmacol. 2001:200-18.
69. Victor YH. Patent ductus arteriosus in the preterm infant. Pediatrics. 1993;35(1):1-4.
70. Rajadurai VS, Yu VY. Intravenous indomethacin therapy in preterm neonates with patent ductus arteriosus. J Paediatr Child Health. 1991;27(6):370-5.
71. Shaffer CL, Gal P, Ransom JL, et al. Effect of age and birth weight on indomethacin pharmacodynamics in neonates treated for patent ductus arteriosus. Crit Care Med. 2002;30(2):343-8.
72. Hammerman C, Aramburo MJ. Prolonged indomethacin therapy for the prevention of recurrences of patent ductus arteriosus. J Pediatr. 1990;117(5):771-6.
73. Rennie JM, Cooke RW. Prolonged low dose indomethacin for persistent ductus arteriosus of prematurity. Arch Dis Child. 1991;66(1):55-8.
74. Tammela O, Ojala R, Iivainen T, et al. Short versus prolonged indomethacin therapy for patent ductus arteriosus in preterm infants. J Pediatr. 1999;134(5):552-7.
75. Edwards AD, Wyatt JS, Richardson C, et al. Effects of indomethacin on cerebral haemodynamics in very preterm infants. Lancet. 1990;335(8704):1491-5.
76. Dumas de la Roque E, Fayon M, Babre F, et al. Minimal effective dose of indomethacin for the treatment of patent ductus arteriosus in preterm infants. Biol Neonate. 2002;81(2):91-4.
77. Kumar RK, Yu VY. Prolonged low-dose indomethacin therapy for patent ductus arteriosus in very low birthweight infants. J Paediatr Child Health. 1997; 33:38-41.
78. van Bel F, Guit GL, Schipper J, et al. Indomethacin-induced changes in renal blood flow velocity waveform in premature infants investigated with color Doppler imaging. J Pediatr. 1991;118(4):621-6.
79. Betkerur MV, Yeh TF, Miller K, et al. Indomethacin and its effect on renal function and urinary kallikrein excretion in premature infants with patent ductus arteriosus. Pediatrics. 1981;68(1):99-102.
80. Yeh TF, Wilks A, Singh J, et al. Furosemide prevents the renal side effects of indomethacin therapy in premature infants with patent ductus arteriosus. J Pediatr. 1982;101(3):433-7.

Citation: *Taha A. S. Clinical and echocardiographic study of the ductus arteriosus in preterm infants. J Preg Neonatal Med. 2024;8(5):221*

81. Brion LP, Campbell DE. Furosemide for symptomatic patent ductus arteriosus in indomethacin-treated infants. Cochrane Database Syst Rev. 2000;(2):CD001148-.

82. Fajardo CA, Whyte RK, Steele BT. Effect of dopamine on failure of indomethacin to close the patent ductus arteriosus. J Pediatr. 1992;121(5):771-5.

83. Lam BC, Wong HN, Yeung CY. Effect of indomethacin on binding of bilirubin to albumin. Arch Dis Child. 1990;65(7):690-1.

84. Herson VC, Krause PJ, Eisenfeld LI, et al. Indomethacin-associated sepsis in very-low-birth-weight infants. Am J Dis Child. 1988;142(5):555-8.

85. Meyers RL, Emil Lln GA, Clyman RI. Patent ductus arteriosus, indomethacin, and intestinal distension: effects on intestinal blood flow and oxygen consumption. Pediatr Res. 1991;29(6):564-74.

86. Fujii AM, Brown E, Mirochnick M, et al. Neonatal necrotizing enterocolitis with intestinal perforation in extremely premature infants receiving early indomethacin treatment for patent ductus arteriosus. J Perinatol. 2002;22(7):535-40.

87. Nakamura T, Tamura M, Kadowaki S, et al. Low-dose continuous indomethacin in early days of age reduce the incidence of symptomatic patent ductus arteriosus without adverse effects. Am J Perinatol. 2000;17(05):271-6.

88. Evans N, Iyer P. Change in blood pressure after treatment of patent ductus arteriosus with indomethacin. Arch Dis Child. 1993;68(5):584-7.

89. Mardoum R, Bejar R, Merritt TA, et al. Controlled study of the effects of indomethacin on cerebral blood flow velocities in newborn infants. J Pediatr 1991; 118:112-5.

90. Colditz P, Murphy D, Rolfe P, et al. Effect of infusion rate of indomethacin on cerebrovascular responses in preterm neonates. Arch Dis Child. 1989;64(1):8-12.

91. Hammerman C, Glaser J, Schimmel MS, et al. Continuous versus multiple rapid infusions of indomethacin: effects on cerebral blood flow velocity. Pediatrics. 1995;95(2):244-8.

92. Bel FV, Bartelds B, Teitel DF, et al. Effect of indomethacin on cerebral blood flow and oxygenation in the normal and ventilated fetal lamb. Pediatr Res. 1995;38(2):243-50.

93. Schmidt B, Davis P, Moddemann D, et al. Long-term effects of indomethacin prophylaxis in extremely-low-birth-weight infants. N Engl J Med. 2001;344(26):1966-72.

94. Szymonowicz W, Yu VY. Periventricular haemorrhage: association with patent ductus arteriosus and its treatment with indomethacin or surgery. Aust Paediatr J. 1986; 23:21-5.

95. Grosfeld JL, Kamman K, Gross K, et al. Comparative effects of indomethacin, prostaglandin E1, and ibuprofen on bowel ischemia. J Pediatr Surg. 1983;18(6):738-42.

96. Van Overmeire B, Smets K, Lecoutere D, et al. A comparison of ibuprofen and indomethacin for closure of patent ductus arteriosus. N Engl J Med. 2000;343(10):674-81.

97. Romagnoli C, De Carolis MP, Papacci P, et al. Effects of prophylactic ibuprofen on cerebral and renal hemodynamics in very preterm neonates. Clin Pharmacol Ther. 2000;67(6):676-83.

98. Varvarigou A, Bardin CL, Beharry K, et al. Early ibuprofen administration to prevent patent ductus arteriosus in premature newborn infants. JAMA. 1996 ;275(7):539-44.

99. Dani C, Bertini G, Reali MF, et al. Prophylaxis of patent ductus arteriosus with ibuprofen in preterm infants. Acta paediatrica. 2000;89(11):1369-74.

100. Ng PC, So KW, Fok TF, et al. Comparing sulindac with indomethacin for closure of ductus arteriosus in preterm infants. J Paediatr Child Health. 1997;33(4):3

101. Ng PC, So KW, Fok TF, et al. Fatal haemorrhagic gastritis associated with oral sulindac treatment for patent ductus arteriosus. Acta Paediatr. 1996;85(7):884-6.

102. Edwards AD, Wyatt JS, Richardson C, et al. Effects of indomethacin on cerebral haemodynamics in very preterm infants. Lancet. 1990;335(8704):1491-5.

103. Colditz P, Murphy D, Rolfe P, et al. Effect of infusion rate of indomethacin on cerebrovascular responses in preterm neonates. Arch Dis Child. 1989;64(1):8-12.

104. Clyman RL. Recommendations for the postnatal use of indomethacin: an analysis of four separate treatment strategies. J Pediatr. 1996;128(5):601-7.

105. Tammela O, Ojala R, Iivainen T, et al. Short versus prolonged indomethacin therapy for patent ductus arteriosus in preterm infants. J Pediatr. 1999;134(5):552-7.

106. Van Overmeire B, Follens I, Hartmann S, et al. Treatment of patent ductus arteriosus with ibuprofen. Arch. Dis. Child. Fetal Neonatal Ed. 1997;76(3):179-84.

107. Varvarigou A, Bardin CL, Beharry K, et al. Early ibuprofen administration to prevent patent ductus arteriosus in premature newborn infants. JAMA. 1996;275(7):539-44.

108. Mosca F, Bray M, Lattanzio M, et al. Comparative evaluation of the effects of indomethacin and ibuprofen on cerebral perfusion and oxygenation in preterm infants with patent ductus arteriosus. J Pediatr. 1997;131(4):549-54.

109. Cassady G, Crouse DT, Kirklin JW, et al. A randomized, controlled trial of very early prophylactic ligation of the ductus arteriosus in babies who weighed 1000 g or less at birth. N Engl J Med. 1989;320(23):1511-6.

110. Mortier E, Ongenae M, Vermassen F, et al. Operative closure of patent ductus arteriosus in the neonatal intensive care unit. Acta Chir Belg. 1996;96(6):266-8.

Citation: *Taha A. S. Clinical and echocardiographic study of the ductus arteriosus in preterm infants. J Preg Neonatal Med. 2024;8(5):221*

111. Förster R. Thoracoscopic clipping of patent ductus arteriosus in premature infants. Ann Thorac Surg. 1993;56(6):1418-20.

112. Kaiser JR, Tilford JM, Simpson PM, et al. Hospital survival of very-low-birth-weight neonates from 1977 to 2000. J Perinatol. 2004;24(6):343-50.

113. Koch J, Hensley G, Roy L, et al. Prevalence of spontaneous closure of the ductus arteriosus in neonates at a birth weight of 1000 grams or less. Pediatrics. 2006;117(4):1113-21.

114. Roberson DA, Silverman NH. Color Doppler flow mapping of the patent ductus arteriosus in very low birthweight neonates: echocardiographic and clinical findings. Pediatr Cardiol. 1994 ;15:219-24.

115. Kääpä P, Seppänen M, Kero P, et al. Pulmonary hemodynamics after synthetic surfactant replacement in neonatal respiratory distress syndrome. J Pediatr. 1993;123(1):115-9.

116. Afiune JY, Singer JM, Leone CR. Echocardiographic post-neonatal progress of preterm neonates with patent ductus arteriosus. J Pediatr (Rio J). 2005;81:454-60.

117. Furzan JA, Reisch J, Tyson JE, et al. Incidence and risk factors for symptomatic patent ductus arteriosus among inborn very-low-birth-weight infants. Early Hum Dev. 1985;12(1):39-48.

118. Mouzinho AI, Rosenfeld CR, Risser R. Symptomatic patent ductus arteriosus in very-low-birth-weight infants: 1987–1989. Early Hum Dev. 1991;27(1-2):65-77.

119. Morales P, Rastogi A, Bez ML, et al. Effect of dexamethasone therapy on the neonatal ductus arteriosus. Pediatr Cardiol. 1998;19:225-9.

120. Feng Ys, Yu V. Management of patent ductus arteriosus in very preterm infants in post-surfactant era. HK J pediatr. 2003; 8:39-100.

121. Siassi B, Blanco C, Cabal LA, et al. Incidence and clinical features of patent ductus arteriosus in low-birthweight infants: a prospective analysis of 150 consecutively born infants. Pediatrics. 1976;57(3):347-51.

122. Skelton R, Evans N, Smythe J. A blinded comparison of clinical and echocardiographic evaluation of the preterm infant for patent ductus arteriosus. J Paediatr Child Health. 1994;30(5):406-11.

123. Walther FJ, Kim DH, Ebrahimi M, et al. Pulsed Doppler measurement of left ventricular output as early predictor of symptomatic patent ductus arteriosus in very preterm infants. Biol Neonate. 1989;56(3):121-8.

124. Maroto E, Fouron JC, Aké E, et al. Closure of the ductus arteriosus: determinant factor in the appearance of transient peripheral pulmonary stenosis of the neonate. J Pediatr. 1991;119(6):955-9.

125. Skinner JR. Why do some babies with a large ductal shunt have a murmur when others do not? In: Skinner JR (ed.) Non-invasive determination of pulmonary arterial pressure in the newborn. MD thesis 1993. University of Leicester, 14:234–49.

126. Alagarsamy S, Chhabra M, Gudavalli M, et al. Comparison of clinical criteria with echocardiographic findings in diagnosing PDA in preterm infants.

127. Iyer P, Evans N. Re-evaluation of the left atrial to aortic root ratio as a marker of patent ductus arteriosus. Arch Dis Child Fetal Neonatal Ed.1994;70(2):112-7.

Citation: *Taha A. S. Clinical and echocardiographic study of the ductus arteriosus in preterm infants. J Preg Neonatal Med. 2024;8(5):221*