A STUDY OF THE PREVALENCE AND CLINICAL CORRELATES OF HAEMODYNAMICALLY SIGNIFICANT PATENT DUCTUS ARTERIOSUS IN LOW BIRTH WEIGHT PRETERM INFANTS AT THE KENYATTA NATIONAL HOSPITAL.

A DISSERTATION PRESENTED IN PART FULFILMENT FOR THE DEGREE OF MASTER OF MEDICINE (PAEDIATRICS)
UNIVERSITY OF NAIROBI
BY
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2007.
DECLARATION

This thesis is my original work and has not been presented for a degree in any other university.

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DEDICATION

This book is dedicated to my wife Lucy and our children Natalie and Kimberlie for their patience and understanding and to my parents William and Esnas Kidaha for their inspiration.
ACKNOWLEDGEMENT

My special thanks go to:-

1. My supervisors Prof. Musoke, Dr. Wamalwa and Dr. Jowi for their guidance, patience and support during the preparation and execution of this study.

2. Dr. C. Jowi for performing echocardiographic evaluation of study patients.

3. Dr Were F. for his assistance and enlightening advice in the study.

4. Stichting, Nederlandse of Netherlands for providing the echocardiography machine used in this study.

5. All parents and infants who participated in the study.

6. The staff of the KNH-newborn unit for their assistance during the study period.

May God bless you all.
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<table>
<thead>
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<tr>
<td>AAo</td>
<td>Ascending Aorta</td>
</tr>
<tr>
<td>AO</td>
<td>Aortic root Diameter</td>
</tr>
<tr>
<td>CS</td>
<td>Coronary Sinus</td>
</tr>
<tr>
<td>DA</td>
<td>Ductus Arteriosus</td>
</tr>
<tr>
<td>hsPDA</td>
<td>Haemodynamically Significant Patent Ductus Arteriosus</td>
</tr>
<tr>
<td>IVC</td>
<td>Inferior Vena Cava</td>
</tr>
<tr>
<td>KNH</td>
<td>Kenyatta National Hospital</td>
</tr>
<tr>
<td>LA</td>
<td>Left Atrium</td>
</tr>
<tr>
<td>LVDDd</td>
<td>Left Ventricular Dimension in Diastole</td>
</tr>
<tr>
<td>LV</td>
<td>Left Ventricle</td>
</tr>
<tr>
<td>LVH</td>
<td>Left Hepatic Vein</td>
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<tr>
<td>MPA</td>
<td>Main Pulmonary Artery</td>
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<tr>
<td>NBU</td>
<td>Newborn Unit</td>
</tr>
<tr>
<td>PDA</td>
<td>Patent Ductus Arteriosus</td>
</tr>
<tr>
<td>RA</td>
<td>Right Atrium</td>
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<tr>
<td>RDS</td>
<td>Respiratory Distress Syndrome</td>
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<tr>
<td>RHV</td>
<td>Right Hepatic Vein</td>
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<tr>
<td>RV</td>
<td>Right Ventricle</td>
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ABSTRACT

Background: Haemodynamically significant patent ductus arteriosus (hsPDA) is a common condition in preterm infants and is associated with considerable morbidity and mortality. Although amenable to both medical and surgical treatment, a limited number of patients are treated at KNH because of under diagnosis in the absence of routine timed echocardiography for preterm infants. At the KNH-NBU, preterm infants who undergo echocardiographic evaluation for PDA are selected based on presence of suggestive clinical signs. The prevalence of hsPDA at the unit is therefore not known.

Objective: To determine the prevalence of haemodynamically significant PDA and its clinical correlates among low birth weight preterm infants.

Design: cross sectional descriptive study.

Setting: The newborn unit of the Kenyatta National Hospital

Methods: Over a three-month period 156 consecutive eligible low birth weight preterm infants aged at least 3 days were recruited into the study. A perinatal history was taken and physical examination done to determine the presence of tachypnea, chest indrawing, and tachycardia, bounding pulses, hyperactive precordium, murmur and hepatomegaly. Echocardiographic evaluation was subsequently done to determine the presence of hsPDA. A haemodynamically significant patent ductus arteriosus (hsPDA) was considered present if a PDA was associated with
a LA: AO ratio of >1.5:1. Those with hsPDA were compared to those without hsPDA with regard to clinical correlates.

Results: Eighty-one (51.9%) preterm infants had a PDA diagnosed by echocardiography. Thirty of those infants with PDA had LA: AO ratio of >1.5:1 giving a prevalence of hsPDA among low birth weight preterm infants of 19.2%. The male to female ratio was 1.5:1, mean birth weight 1635 (1233-2047) g, mean gestational age 31.5 (29.3-33.7) weeks and median postnatal age of 5 days (IQR 4-11). Of the 30 infants with hsPDA, 10 (33.3%) had clinically diagnosed PDA. Clinical signs had low positive predictive values with the most predictive signs being hyperactive precordium 46.2%, murmur (systolic or continuous) 43.8% and bounding peripheral pulses, 40.5%.

Conclusion: The echocardiographic prevalence of hsPDA was 19.2% with only a third of these diagnosed clinically. Therefore, although haemodynamically significant PDA is common in this unit, reliance on clinical signs alone leads to underdiagnosis. Improved availability and utilization of echocardiography in the unit will enhance the diagnosis and management of patients with hsPDA.
INTRODUCTION AND LITERATURE REVIEW

Neonatal mortality accounts for 65% of all infant deaths and 37% of child deaths worldwide. Major causes of neonatal mortality are diseases associated with preterm birth, low birth weight and lethal congenital anomalies. Globally, preterm births account for 28% of neonatal deaths. Other major causes of neonatal deaths include severe infections, 26% and birth asphyxia 23%.¹ In Kenya, the infant mortality rate is 77/1000 live births with neonatal mortality contributing 42% of these. In addition, 82% of the neonatal deaths that occur locally are perinatal.² Since most neonatal deaths occur in the first week, prompt diagnosis of neonatal diseases and institution of the required therapy is central to ensuring improved survival and reduced morbidity among neonates.

Prematurity is a major cause of morbidity and mortality in the newborn period largely due to susceptibility of preterm infants to various medical conditions as a result of general underdevelopment of organ systems. Patent ductus arteriosus is a major cause of morbidity in preterm infants. It is associated with short-term complications including necrotizing enterocolitis and intraventricular hemorrhage as well as long term morbidity like periventricular leukomalacia. Two meta-analyses of 10-14 randomized control trials on prophylactic closure of PDA using indomethacin showed a reduced incidence of intraventricular haemorrhage and reduced neonatal mortality rate. ⁵,⁶ Cassady et al ⁷ in
a study of prophylactic closure of PDA within 5 days after birth showed in randomized control trials a reduction in the incidence of necrotizing enterocolitis (8% vs. 30%). PDA also causes poor growth in low birth weight preterm infants. 3, 4, 51 The key to reducing morbidity and mortality associated with PDA is the identification and prompt treatment of that which is haemodynamically significant (hsPDA). This is defined as an abnormally persistent ductus arteriosus producing clinical symptoms of cardiac and respiratory instability and poor growth. HsPDA is also defined by echocardiographic indices known to have poor prognosis i.e. LA: AO ratio of >1.5:1. 34

The ductus arteriosus is a vascular connection between the main pulmonary artery and the aorta. It develops from the distal portion of the left sixth aortic arch. The ductus arteriosus carries between 55 and 60 percent of the combined ventricular output, thereby permitting flow to be diverted away from the high resistance pulmonary circulation to the descending aorta and the low resistance placental circulation. 8

Fig 1 below shows fetal circulation with a preferential pattern of ventricular output. The left ventricle (LV) receives blood from the left atrium and directs 90 percent via the ascending aorta to the highly metabolic heart and upper part of the body. Only 10 percent of the blood from the ascending aorta flows across the isthmus to the descending aorta. The right ventricle (RV) receives right atrial blood (RA) and ejects it via the main pulmonary artery. The pulmonary
arterial circulation is vasoconstricted, therefore only 10 percent of right ventricular outflow enters the lungs. The major portion of this blood (90%) bypasses the lungs and flows through the ductus arteriosus into the descending aorta. Approximately 65 percent of this blood returns to the placenta while the rest perfuses fetal organs and tissues.

Figure 1. The ventricular outflow pattern in fetal circulation

Figure 2 below shows the preferential pattern of venous return to the right ventricle (RV) and the left ventricle (LV). The more saturated blood (dark arrow) from the umbilical vein (U.V) passes via the ductus venosus (D.V) and the left hepatic vein (LHV) to the left atrium (LA) and left ventricle. The less saturated blood (light arrow) from the lower body via the inferior vena cava (IVC) from the portal sinus from the coronary sinus (CS) and from the superior vena cava (SVC) passes to the right atrium and right ventricle. 9
After birth, there are circulatory changes that include closure of the fetal shunts, including the ductus arteriosus. The postnatal closure of the ductus is effected in two phases. In the first phase, which occurs immediately after birth, contraction and cellular migration of medial smooth muscles in the wall of the ductus arteriosus produce shortening, increased wall thickness and protrusion into the lumen resulting in functional closure. The second phase also called the anatomical closure involves the folding of the endothelium, disruption and fragmentation of the internal elastic lamina and proliferation of
subintimal layers. Connective tissue proliferation and replacement of muscle fibers with fibrosis result in permanent sealing of the lumen to produce ligamentum arteriosum. A patent ductus arteriosus occurs when there is failure in the mechanisms of closure.

Healthy preterm infants without respiratory distress syndrome undergo spontaneous functional closure of the ductus arteriosus in the first four days after birth at comparable rates. Reller et al\textsuperscript{11} found that 94% of preterm infants without RDS had a patent ductus arteriosus on day 1, 44% on day 2, 15% on day 3 and 2% on day 4. Evans et al\textsuperscript{12} found that ductal shunting persisting for more than 3-4 days is unusual in healthy preterm infants.

Mouzinho et al\textsuperscript{13} in a study of low birth weight infants found clinically significant PDA beyond day 4 in 20% of infants less than 1750g birth weight. The study also found that infants with birth weight 500-999g, 1000-1499, and 1500-1750g had clinically significant PDA identified in 42%, 21% and 7% respectively.

Preterm infants with RDS have a higher incidence of PDA especially those with respiratory failure requiring assisted ventilation.\textsuperscript{45} Eleven percent of infants born at 30-37 weeks gestation who had uncomplicated RDS were found to have a PDA on day 4. \textsuperscript{46} Dudell et al\textsuperscript{16} in a study of preterm infants requiring assisted ventilation, found the incidence of PDA on day 1 to be 90%, reducing by day 3 to 60% for those with a birth weight of less than or equal to 1500g and 40% for
those over 1500g. This study showed that the spontaneous PDA closure rate plateaued at 3 days of age in these infants with respiratory failure.

There are three patterns of occurrence of PDA. The first and commonest is the isolated PDA of prematurity. In this case the PDA occurs without any associated structural cardiac defects in a preterm infant. The other type of PDA occurs in association with cardiac structural abnormalities. These anomalies include obstructive lesions of the left or right outflow tract or ventricular septal defects. The third type of PDA is the abnormally structured ductus arteriosus that usually occurs in term infants but may also be associated with recognized malformation syndromes e.g. congenital rubella syndrome. This study focused on the isolated PDA of prematurity.

THE DETERMINANTS OF CLINICAL MANIFESTATION OF PDA

The clinical presentation of PDA are varied and determined by the degree of shunting across the ductus arteriosus. This is determined by the size and shape of the ductus arteriosus, the pulmonary pressure and the patient's age at diagnosis. The variables in the ductus that alter the clinical findings are of course, all interacting and usually cannot be separated; however they do have some distinguishing features when they occur as isolated variations.

Pulmonary Pressure and PDA

The alteration in clinical findings due to changes in pulmonary resistance overshadows the effect of all other variables on the clinical
features of PDA. The higher the pulmonary resistance, the less the overall flow through the ductus arteriosus in a left to right shunt. Conversely, in a right to left shunt through a PDA, the higher the pulmonary resistance the greater the flow through the PDA. The right to left shunt occurs predominantly in cases of persistent fetal circulation. Elevation of pulmonary pressure above systemic pressures produces right to left shunting at the ductus arteriosus with differential cyanosis pathognomonic of persistent fetal circulation.  

PDA size and Clinical Presentation

The smaller the ductus, usually the higher the pitch and the more localized is the continuous murmur. In addition, the other clinical signs are less prominent with very small ductus arteriosus. Unless there is associated increased pulmonary vascular resistance, the larger the ductus the more prominent are the associated signs. Evans et al 18 in a study of longitudinal changes in the diameter of the ductus arteriosus in ventilated preterm infants showed that a ductal diameter of less than or equal to 1.5mm was associated with normal antegrade postductal aortic diastolic flow, but when it was greater than 1.5mm, absent or retrograde postductal aortic diastolic flow is usually present. It is this retrograde postductal flow that is responsible for the diastolic steal phenomena that has been shown to result in significant reduction in visceral blood flow that explains the high incidence of necrotizing enterocolitis in patients with PDA. 19
CLINICAL MANIFESTATIONS OF PDA

A high parasternal systolic or continuous murmur is an important sign of PDA. The typical continuous murmur is not usually present in most cases especially in preterm infants. The murmur is usually systolic due to high pulmonary resistance. Some studies have shown that a murmur is audible in only 20-50% of infants with a documented PDA. A murmur is not always present even in the presence of a significant duct. Skelton et al showed that it is unreliable for both diagnosis and prognosis. Musoke et al in a study of 537 infants below 2000g found that 8.9% had murmurs suggestive of PDA. The relatively low incidence of PDA was partly attributed to under diagnosis.

Bounding peripheral pulses is another manifestation of PDA. It refers to the clinical impression of a wide pulse pressure. This sign has limited diagnostic utility as some studies have shown that it correlated poorly with the actual presence of a duct and demonstrated no correlation with haemodynamic significance. In addition this sign has not been substantiated by objective clinical data arterial blood pressure data.

An active heaving precordium is also a manifestation of a PDA. Kufershmidt et al found it to be the most sensitive diagnostic sign and most predictive for a hsPDA.

If a shunt is allowed to become sufficiently large, clinical evidence of left ventricular failure may appear. This includes recurrent apnoea,
tachycardia, tachypnoea and rales on auscultation of the lung fields. Increased pulmonary blood flow leads to the development of pulmonary edema. The latter causes carbon dioxide retention and increased oxygen dependence especially in mechanically ventilated infants. A deterioration in ventilatory status as indicated by lack of progress in weaning or worsening oxygen and ventilatory requirements can be a manifestation of hsPDA.\textsuperscript{32}

In some rare very low birth weight infants, there may be absence of clinical signs indicative of ductal opening. This type of PDA is called the silent ductus.\textsuperscript{33}

**COMPPLICATIONS OF hsPDA**

Early diagnosis and treatment has been shown to reduce complications associated with hsPDA.\textsuperscript{48} These complications are multisystemic in view of the circulatory changes that occur in patients with hsPDA. There is a decrease in aortic blood flow during diastole (diastolic steal phenomenon) resulting in multiorgan hypoperfusion in diastole.

**Congestive cardiac failure and hsPDA**

In patients with hsPDA, the left ventricular output is increased in early phase due to increased stroke volume. This increase is however not sustainable and congestive cardiac failure ensues. The presence of tachypnea, tachycardia, gallop rhythm, cardiomegaly, rales and
hepatomegaly indicate congestive cardiac failure. Congestive cardiac failure is a late manifestation of hsPDA. Musoke et al found that 27% of the patients with PDA had congestive cardiac failure.

RDS and hsPDA

Infants with respiratory distress syndrome complicated by hsPDA have delayed recovery. Left to right shunt increases the amount fluid and protein movement from the pulmonary blood vessels into the interstitium. This increases the work of breathing and the risk of development of chronic lung disease. The closure of hsPDA has been shown to lead to significant improvement in pulmonary compliance.

Growth failure and hsPDA

Infants need to maintain linear growth and weight gain for optimum outcome. Infants with large left to right shunt e.g. hsPDA and large VSD have been shown to have greater degree of growth impairment than those with small shunts. Nehgme et al showed that infants had a shorter time to regain birth weight if the hsPDA was closed pharmacologically.

Necrotizing enterocolitis and hsPDA

The diastolic steal phenomenon has been shown to result in significant reduction in blood flow to the midgut. This probably explains the high incidence of necrotizing enterocolitis in infants with hsPDA. Prophylactic ligation of the PDA has been shown to reduce the incidence of necrotizing enterocolitis from 30% to 8%.
Periventricular leukomalacia and hsPDA

Infants with hsPDA were reported to be more likely to develop periventricular leukomalacia (PVL) than those without hsPDA. Infants with PVL were also shown to have a higher incidence of retrograde flow during diastole in the anterior cerebral artery.\(^{21}\)

Other complications of PDA include aneurism of the ductus, pulmonary vascular disease and infective endocarditis.
DIAGNOSTIC EVALUATION OF PDA

Chest radiography

The chest radiograph will show parenchymal changes of respiratory distress syndrome, cardiomegaly and pulmonary plethora. Abnormalities are difficult to interpret in the presence of parenchymal lung disease. Cardiomegaly is variable especially with an infant on artificial ventilation. Increasing cardiomegaly indicates an increasing shunt. Plethoric lung fields, cardiomegaly and prominent left atrium occur with significant volume overload. Cardiomegaly occurs in up to 75% of cases of PDA but does not correlate highly with significant PDA. Cardiomegaly and lung haziness are a better predictor of significant PDA than cardiomegaly alone. Ellison et al. found that chest radiography had a sensitivity of 30% for diagnosis of hsPDA. Chest radiography for diagnosis of hsPDA in the presence of hyaline membrane disease is at best of debatable value. In the very low birth weight infants with lung disease there may be difficulty in defining the cardiac silhouette and the different cardiac chambers on plain radiography. Increased pulmonary vascularity is difficult to distinguish separately from parenchymal lung changes.
Electrocardiogram (ECG)

In preterm infants with a large PDA, the ECG shows left atrial enlargement and left ventricular hypertrophy. Cooksey et al \(^{36}\) found left ventricular hypertrophy in 59% of patients with PDA. This study also showed that the correlation of left ventricular weight with various measures from ECG indicated a positive predictive value of only 60%. Infants with hsPDA also demonstrate moderate repolarization disturbances as well. These include depressed ST segment in V1 in 59%, elevated ST segment in V6 in 26% of the patients and T-wave inversion in 15% of the patients. These occur as a result of volume overload of the left ventricle and concomitant, diastolic "coronary steal".

The criteria for right and left atrial enlargement are the same for premature infants as full-term infants but the criteria for right and left ventricular hypertrophy are different. Rowe et al \(^{44}\) suggests that an R/S in V1 less than 1 after 2 days or less than 0.6 after 7 days suggests left ventricular hypertrophy. Fowler et al \(^{37}\) found that it is difficult to be sure about the accuracy of these criteria since there are not large groups of normal preterm infants at various birth weights to form a foundation for good criteria for chamber enlargement. The ECG has a limited role in the diagnosis of hsPDA based on its low positive predictive value and questionable accuracy in preterm infants.
ECHOCARDIOGRAPHY

This provides both anatomic and haemodynamic assessment of ductus arteriosus. There are several categories of ultrasound methods for the diagnosis of PDA. These include M-mode echocardiography, two-dimensional or cross-sectional echocardiography, color flow Doppler echocardiography and contrast echocardiography. The current echocardiography machines apply several of these modes echocardiography serially in the diagnosis of PDA. For instance, for a given patient, M-mode determinations are done to define chamber size and indirect quantification of flow across shunts. This is then followed by a 2-D echo which gives a 2 dimensional view of the heart/structure defect then finally a color flow Doppler study is done to determine the direction of blood flow across the defect and quantify the pressure driving the flow. Although here they are discussed separately in practice they are applied concurrently to improve the diagnostic yield.

M-mode echocardiography

The sensitivity of the individual M-mode measurements in the diagnosis of PDA varies from 52-71 %. \(^{31}\) Left to right ductal shunt increases the volume load on the left side of the heart and dilates the left atrium. The ratio of the diameter of the left atrium, to that of the aortic root (LA: AO) ratio is the most widely used M-mode measurement. A LA: AO ratio of >1.5:1 is indicative of haemodynamically significant PDA. The predictive value of LA: AO ratio...
increases to 88% for scans done after the first day of life for the diagnosis of hsPDA. False positives have been reported in infants with poor myocardial function with an enlarged left ventricle and left atrium; a heart murmur from atrioventricular valve regurgitation and radiological abnormalities of cardiomegaly and pulmonary plethora. The systolic time integrals help distinguish between such infants and those with PDA. With decreased contractility, the left pre-ejection period to left ventricular ejection time (LPEP/LVET) is increased but in PDA this is decreased. Left heart dimension combined with systolic time intervals give the best discrimination between PDA and no PDA.

Despite its wide use, it should be noted that M-mode echocardiography is not commonly used in isolation but as an adjunct to other modes of echocardiography. This is because M-mode does not involve direct visualization of the ductus.

2- Dimensional Echocardiography

This is also called cross-sectional echocardiography. Left ventricular size and left ventricular activity can be assessed accurately with this method. The dynamics of both left ventricular and descending aortic wall motion also can give an indication of the magnitude of the shunt. Direct visualization of the ductus arteriosus is usually possible and confirms the diagnosis. Gutgesell et al in assessing the accuracy of cross-sectional echocardiography alone (without the aid of Doppler) in
the diagnosis of the newborn heart disease in 126 patients who subsequently underwent cardiac catheterization and angiography found that 87% of the lesions were accurately predicted by echocardiography alone. However most errors were due to overlooking information that was already on videotape.

**Doppler Echocardiography**

Doppler techniques are applied to the evaluation of flow patterns in infants with PDA. These include pulsed, continuous wave and color flow Doppler. Flow from the aorta into the pulmonary artery can be detected and velocity profiles of flow in the main pulmonary artery, ductus arteriosus and descending aorta in infants with PDA have been characterized. ³⁸

One method of assessing shunt size involves pulsed Doppler assessment of flow in the aortic arch before and after the ductal insertion. The presence of reversed diastolic flow in the descending aorta indicates that the PDA is likely to be of haemodynamic significance. This can be quantified by measuring the ratio of the velocity time integrals of the retrograde diastolic and antegrade systolic flow. This method has been validated against invasive measures of shunt size. ⁴¹

The most accurate method is the direct imaging of the PDA with direct pulsed wave or color flow Doppler. It allows for visualization of the extent of flow disturbance in the main pulmonary artery and the
direction of flow jet. Estimates of pulmonary arterial pressure can also be made. ¹⁴²

Doppler echocardiography is rarely used alone but in combination with cross-sectional (2-D) echocardiography. Leung et al ¹⁴³ studied 140 consecutive neonates using combined cross-sectional and pulsed Doppler. There were 33(5%) diagnostic errors of which 23 were missed or uncertain diagnosis and 10 wrong interpretations. The diagnostic sensitivity and specificity for the combined non-invasive technique was 96% and 98% respectively.
PROBLEM STATEMENT AND STUDY JUSTIFICATION

Haemodynamically significant PDA is the commonest cardiovascular illness among preterm infants. It is also amenable to both medical and surgical treatment. The key to reducing the attributable morbidity lies in enhanced and timely diagnosis and treatment. The prevalence of the PDA has been noted to rise in centers with improved survival of preterm infants. In these centers, the improved diagnosis of hsPDA by a routine-timed echocardiography of preterm infants leads to enhanced diagnosis and treatment. At the KNH, echocardiography is not done routinely on all low birth weight preterm infants admitted at the newborn unit. Instead it is undertaken only when clinical signs suggest the presence of a hsPDA. A previous study at this unit based on the presence of clinical signs of PDA found lower prevalence compared to centres where routine echocardiography is done. This low prevalence was attributed to underdiagnosis and therefore the disease burden of hsPDA at KNH is probably underestimated. This study seeks to define the prevalence of hsPDA using echocardiographic criteria thereby identify missed opportunities for treatment of hsPDA at KNH. The study also seeks to describe the clinical correlates of hsPDA with a view of suggesting measures to enhance its diagnosis.
RESEARCH QUESTION
What is the prevalence and clinical correlates of haemodynamically significant patent ductus arteriosus (hsPDA) among low birth weight preterm infants at the Kenyatta national hospital newborn unit?

STUDY OBJECTIVES

PRIMARY OBJECTIVE
To determine the prevalence of haemodynamically significant PDA among low birth weight preterm infants at the Kenyatta national hospital- Newborn unit.

SECONDARY OBJECTIVE
To determine the clinical correlates of haemodynamically significant patent ductus arteriosus among low birth weight preterm infants at the Kenyatta national hospital-Newborn unit.

ETHICAL CONSIDERATION
A copy of the dissertation protocol was submitted to the ethical and research committee of the KNH and permission to carry out the study granted. Informed consent was obtained from parent/guardian of each infant before they were recruited into the study.
MATERIALS AND METHODS

This was a descriptive, cross sectional study carried out at the Kenyatta national hospital newborn unit over a 3 -months period among low birth weight preterm infants aged 3 days and above admitted to the unit.

STUDY AREA

KNH is one of the two public tertiary hospitals in Kenya and also serves as a teaching hospital for the Nairobi University College of health sciences. It also serves as a primary and secondary health facility for the city of Nairobi (estimated population 2 million).

Most of the patients admitted to the newborn unit are those delivered at the KNH labor ward. The rest of the patients are referred from other hospitals. As a hospital policy, all the newborn infants weighing less than 2000g are admitted to the unit. Those with birth weight over 2000g and are ill are also admitted to the NBU. Those over 2000g and are stable are not admitted to the newborn unit unless the mother is seriously ill.

At the time of conducting this study there were no facilities for mechanical ventilation at the KNH -NBU.
STUDY POPULATION

The study population comprised of low birth weight preterm infants aged at least 3 days. An infant was considered to have a hsPDA if a PDA was associated with a LA: AO ratio of >1.5:1 demonstrated by echocardiography.

STUDY PERIOD

March 2007 to May 2007

INCLUSION CRITERIA

1. Low birth weight preterm infants weighing less than 2500g
2. Age of 3 days and above
3. Gestational age at birth less than 37 weeks by dates from the first day of the last menstrual period or by modified Ballard score.
4. Parent & guardian’s informed consent

EXCLUSION CRITERIA

(i) Infants found to have a coexisting anatomic congenital heart disease at echocardiography.
(ii) Neonate with major congenital malformation.
(iii) Neonates who died before evaluation by echocardiography.
SAMPLE SIZE

This was calculated using the formula

\[ n = \frac{Z^2 P(1-P)}{d^2} \]

Where

- \( n \) is the minimum sample size of low birth weight preterm infants
- \( Z \) is the value for the standard normal deviate which corresponds to a 95% confidence interval (two tailed) which is \( = 1.96 \).
- \( P \) is the prevalence of haemodynamically significant PDA among 130 preterm infants 30-37 weeks gestation at birth who were not mechanically ventilated in a study by Ellison et al. \(^{46}\)
- \( d \) is the degree of precision, 5%.

Substituting

\[ n = \frac{1.96^2 \times 0.11 \times 0.89}{0.05 \times 0.05} \]

\[ n = 150 \]
INVESTIGATION TOOLS

A standard examination form was utilized to collect both clinical and echocardiographic information. Appendix I shows the data entry form which was used to record perinatal events and physical signs. Rowe et al guidelines for diagnosis of heart failure in the neonate were used to identify infants with congestive cardiac failure as shown in appendix 4. 44

SAMPLING PROCEDURE

Consecutive enrolment of all infants meeting the inclusion criteria was done until the desired sample size was reached.

INVESTIGATION PROCEDURE

All infants admitted to the newborn unit are weighed soon after delivery. Low birth weight infants admitted to the newborn unit were identified. The gestational age at birth was calculated from the first day of the last menstrual period (LMP) and where the LMP was unknown or in doubt, the New Ballard Score (Appendix 2) was used to determine the gestational age at birth. 47

The parent or guardian of low birth weight preterm infant aged 3 days and above were approached and informed consent was obtained. Those enrolled in the study had antenatal and perinatal history taken. The maternal medical record was used to verify antenatal data. The maternal antenatal and perinatal events identified included, maternal
antenatal illness, antenatal corticosteroid use etc are shown in Appendix 1.

Infants aged 3 days and above had a physical examination done by the investigator to identify the presenting clinical signs are shown in Appendix 1. These included the heart rate, respiratory rate, and presence of chest retraction, gallop rhythm, bounding pulses, hyperactive precordium, murmurs and hepatomegaly. An experienced pediatric cardiologist validated the physical examination findings. The infant’s medical record was used to identify some clinical parameters e.g. mode of feeding, volumes of feeding, diagnosis at admission, clinical suspicion of PDA by the primary clinician(s) was also documented and hemoglobin level.

In order to avoid bias, physical examination was done and findings documented before echocardiographic evaluation. A pediatric cardiologist, Dr. Jowi within 6 hours after physical examination, performed an echocardiographic evaluation. This was done using vivid I, Netherlands portable ultrasonoscope using an infant probe. This machine had multiple modes of echocardiography. These include M-mode, cross-sectional or 2D- echocardiography and color flow Doppler echocardiography. These three modes were undertaken serially for each infant in the study. The evaluation was at the site of care of the infant i.e. incubator or cot without need to move the patient from the NBU.
The ultrasonoscope had functions to perform 2-Dimensional, M-mode and color flow Doppler studies. The ductus arteriosus was visualized using the parasternal short axis and suprasternal view and its dimension assessed in the two views. The transducer was positioned in the third or fourth left intercostal space to locate maximum mitral valve excursion. A sweep of the transducer beam was then done within the left ventricle from its body to the aortic root. When suitable view was obtained, the left atrial (LA) and aortic root (Ao) dimension were determined. The left atrial dimension was determined at the end systole as the distance between the outer edge of the posterior aortic root echo and the endocardial echos of the left atrial wall. Measurements were made only in an area where the aortic cusp tissue was observed as well as an area where there was a discrete left atrial echo. The aortic root (AO) dimension was measured as the distance between the outer walls of the aortic root at end systole. It is from these LA and AO that the LA: AO ratio was determined as shown in illustration 1 below.
Illustration 1. The above diagram shows the ultrasound method for determination of the magnitude of a shunt through PDA using M-mode measurements. A 2-Dimensional echocardiogram was done to localize the aorta (AO) and the left atrium (LA). The dimension of the left atrium and the root of the aorta were taken as shown by the perpendicular arrows. The LA: AO ratio was then computed. In this preterm infant the LA: AO ratio was 1.04:1 which was not significant. A LA: AO ratio of >1.5:1 was considered significant.
By aid of color flow Doppler studies a patent ductus arteriosus was visualized and its dimension determined. A PDA was considered significant if it was associated with an LA: AO ratio of >1.5:1. A complete echocardiographic evaluation was done to exclude structural defects of the heart as well as determination of ejection fraction, fractional shortening and pulmonary artery pressure. The results were entered into an echocardiographic evaluation form (Appendix 3)

DATA ANALYSIS

The clinical and echocardiographic data collected was entered in a computer using the SSPS program. Descriptive statistics including rates and percentages were determined during the analysis. Infants were categorized as having hsPDA and not having hsPDA. The differences between the two groups were assessed using the Chi-square test and odds ratio (for categorical variables) and Mann-Whitney U or independent t-test (for continuous variables). Univariate correlates of the presence of hsPDA were determined using the Chi square test and Fishers exact test. The level of significance was set at p <0.05. The denominator for calculation of prevalence was the total number of infants screened echocardiographically and met the inclusion criteria. Analysis was also done in strata of birth weight and gestational age. The following strata of weight were used: <999g, 1000-1500g, 1501-1750g, and 1701-2499g. The associations were compared using odds ratio and the level of significance also stated.
Descriptive data was also analyzed and presented in proportions and frequency tables. The means are stated with the corresponding $\pm 1$ standard deviation and standard error. The median and the corresponding interquartile range are stated for skewed data. The results were presented in descriptive form using frequency tables, graphs and cross tabulation.
RESULTS

The prevalence of haemodynamically significant patent ductus arteriosus (hsPDA) among low birth weight preterm infants was 19.2%. Of the 162 low birth weight preterm infants who met the clinical inclusion criteria, 6 were excluded because they were diagnosed to have congenital structural heart disease on echocardiography. Three had ventricular septal defects, one had a combination of ventricular septal defect and atrial septal defect, one had cor triatriatum and one had a left atrial tumour. The total number of infants who met the clinical and echocardiographic criteria for enrollment in the study was 156. Of these, 81 (51.9%) had a PDA on echocardiography while 30 (19.2%) had hsPDA. The infants with hsPDA were 37.5% of those diagnosed with PDA. The male to female ratio of infants with hsPDA was 1.5:1. Figure 3 below shows the flow of patients during the study.

![Flow diagram of study patients.](image-url)
Table I: Demographic Characteristics of study patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>All n=156</th>
<th>hsPDA n=30</th>
<th>No hsPDA=126</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male: female</td>
<td>1:1</td>
<td>1.5:1</td>
<td>1:1.03</td>
<td>0.288</td>
</tr>
<tr>
<td>Mean birth weight/g.</td>
<td>1780(356.9)</td>
<td>1635 (412)</td>
<td>1726(341.9)</td>
<td>0.210</td>
</tr>
<tr>
<td>Mean gestational age (weeks)</td>
<td>32 (2.2)</td>
<td>31.50 (2.2)</td>
<td>32.51 (2.5)</td>
<td>0.02</td>
</tr>
<tr>
<td>Median postnatal age (days)</td>
<td>5</td>
<td>4.5</td>
<td>5</td>
<td>0.059</td>
</tr>
<tr>
<td>Mean surface Area/m²</td>
<td>0.13 (0.1)</td>
<td>0.131(0.02)</td>
<td>0.13(0.02)</td>
<td>0.266</td>
</tr>
<tr>
<td>Mean hemoglobin,g/dl</td>
<td>13.21(2.03)</td>
<td>13.27(1.90)</td>
<td>13.21(2.0)</td>
<td>0.102</td>
</tr>
<tr>
<td>Mean fluid intake/kg/24hr</td>
<td>153.4(25.3)</td>
<td>142.3(26.6)</td>
<td>156.7(30.5)</td>
<td>0.025</td>
</tr>
</tbody>
</table>

KEY: #-Chi-square, * student t test, ** Mann-Whitney-U test

Table I shows the comparison of some of the demographic characteristics of study patients. The means are compared for normally distributed data and are stated with their corresponding standard deviation () while the median with the interquartile range (IQR) is stated for skewed data. There was no statistically significant difference in the male to female ratio, mean birth weight, mean surface area and median postnatal age for those with hsPDA and those without hsPDA. There was
also no difference in the mean hemoglobin of infants with hsPDA and those without. Infants with hsPDA had a statistically significant lower mean gestational age at birth compared to their counterparts without hsPDA. Infants without hsPDA were on a higher fluid volume regimen in the preceding 24 hours compared to those with hsPDA. The fluid intake here refers to total parenteral and oral intake. The infants without hsPDA were tolerating larger volumes of feeds compared to those with hsPDA.
Table II
Distribution of hsPDA by, sex, Birth weight and Gestational age. (N=156)

<table>
<thead>
<tr>
<th></th>
<th>hsPDA Present n=30</th>
<th>Absent n=126</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>sex</strong></td>
<td>NO. (%)</td>
<td>NO. (%)</td>
</tr>
<tr>
<td>Female</td>
<td>12 (40)</td>
<td>64 (50.8)</td>
</tr>
<tr>
<td>Male</td>
<td>18 (60)</td>
<td>62 (49.2)</td>
</tr>
<tr>
<td><strong>Birth weight (g)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;999</td>
<td>0</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td>1000-1499</td>
<td>14 (46.7)</td>
<td>28 (22.2)</td>
</tr>
<tr>
<td>1500-1750</td>
<td>5 (16.7)</td>
<td>43 (34.1)</td>
</tr>
<tr>
<td>1751-2000</td>
<td>5 (16.7)</td>
<td>32 (25.4)</td>
</tr>
<tr>
<td>&gt;2000</td>
<td>6 (20.0)</td>
<td>22 (17.5)</td>
</tr>
<tr>
<td><strong>Gestational Age (weeks)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;27</td>
<td>0</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td>28-29</td>
<td>5 (16.7)</td>
<td>4 (3.2)</td>
</tr>
<tr>
<td>30-31</td>
<td>11 (36.7)</td>
<td>24 (19.0)</td>
</tr>
<tr>
<td>32-33</td>
<td>5 (16.7)</td>
<td>52 (41.3)</td>
</tr>
<tr>
<td>34-36</td>
<td>9 (30)</td>
<td>45 (35.7)</td>
</tr>
</tbody>
</table>

Table II above shows the distribution of infants with hsPDA according to sex, birth weight and gestational age at birth. The highest prevalence was in the very low birth weight category. There was increasing prevalence with decreasing gestational age (Pearson coefficient \( r = -2.69 \) \( p < 0.01 \)). Six infants (20%) of those with hsPDA compared with 17.5% those without hsPDA weighed more than 2000g.

The distribution by birth weight is represented by the bar chart below (Figure 4).
Figure 4: Distribution of hsPDA by birth weight

Note: The figures above the bars are percentages.

Figure 4 above shows the highest prevalence in the weight category of 1000-1499g. It also shows a high prevalence in those above 2000g of 21.4%. There was only one infant with birth weight under 1000g.
ECHOCARDIOGRAPHIC FEATURES OF STUDY PATIENTS.

Of the 156 low birth weight infants who were screened, 81 (51.9%) showed evidence of a patent ductus arteriosus. Of the patients with PDA only 30 (37.5%) had an associated LA: AO ratio of >1.5:1 consistent with hsPDA. There was wide variation in the size of PDA among study patients. The largest PDA measured 6.8mm while the smallest was 1.2mm. The mean PDA diameter was 2.85±1.22mm. Infants with haemodynamically significant patent ductus arteriosus had a statistically significant larger mean PDA diameter, 3.35±1.2mm compared to those without hsPDA, mean PDA diameter of 2.5±1.15mm (p<0.05). Examples of the echocardiographic findings in some of the patients are shown in the illustrations 2-7 below.
Illustration 2. This a parasternal short axis view showing a large PDA. The PDA diameter was 4mm and the associated LA:AO ratio was 1.79:1. This was an example of a haemodynamically significant patent ductus arteriosus (hsPDA). The related structures are as follows: AO = Aorta, PA = Main Pulmonary artery, RA = Right atrium, LA = Left atrium, rpa = right pulmonary artery, Lpa = left pulmonary artery.
Illustration 3. Echocardiogram of a male preterm infant, birth weight of 1200g. This is a 2-Dimension with color flow Doppler echocardiogram showing the flow across a PDA (above). The diagram also in the lower aspect shows a velocimetry of the flow across the PDA. The flow is continuous i.e. both systolic and diastolic.
Illustration 4. This echocardiogram of a 20-day-old male preterm infant with a birth weight of 1700g and a weight of 1900g at the time of evaluation. It shows the estimation of pulmonary pressure using the flow across the tricuspid valve. The infant had moderate pulmonary hypertension of 52.61mmHg. The infant also had a 2.5mm PDA with an associated LA: AO ratio of 1.5:1.
Illustration 5.

This is parasternal view of the right atrium (RA) and the left atrium (LA) of the same infant in illustration 4 above. It shows a patent foramen ovale with the color flow Doppler indicating flow across the opening. This together with the pulmonary hypertension and PDA constitute persistent fetal circulation.
Illustration 6 above shows a suprasternal view color flow Doppler echocardiograph of study participant no 101. The PDA diameter was 2.3mm. The associated LA: AO ratio was 1.04:1 and was not considered as a haemodynamically significant PDA (hsPDA).
ILLUSTRATION 7: STUDY NO. 99

Illustration 7 shows a suprasternal view of a Doppler echocardiogram of participant no. 99. It shows an example of a large PDA with a diameter of 5.3 mm. The associated LA: AO ratio was 1.8:1 and was considered to be a hsPDA.
<table>
<thead>
<tr>
<th>Variable</th>
<th>All n=156</th>
<th>hsPDA present</th>
<th>hsPDA absent</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean pulmonary pressure/mmHg</td>
<td>32.43(16.7)</td>
<td>45.41(17.4)</td>
<td>29.24(9.0)</td>
<td>&lt;0.05*</td>
</tr>
<tr>
<td>Pulmonary hypertension &gt;30mmHg</td>
<td>64 (41.0%)</td>
<td>24 (79.3%)</td>
<td>40 (32%)</td>
<td>&lt;0.05#</td>
</tr>
<tr>
<td>Mean fractional shortening %</td>
<td>34.0(8.8)</td>
<td>34.6(7.0)</td>
<td>33.93(9.2)</td>
<td>0.725*</td>
</tr>
<tr>
<td>Mean ejection fraction %</td>
<td>65(11.3)</td>
<td>65.65(11.2)</td>
<td>65.49(11.4)</td>
<td>0.947*</td>
</tr>
</tbody>
</table>

* Student t test    # chi square test

The means are indicated with their corresponding one standard deviation ().

Table III above shows that the mean pulmonary pressure in infants with hsPDA was significantly high compared with infants without hsPDA whose mean was 29±14.9mmHg SE 1.4. The difference in the means was statistically significant (p<0.05) Pulmonary hypertension was more prevalent in infants with hsPDA (79.3%) than those without hsPDA. In 9(14%) infants the pulmonary hypertension occurred in association with persistent fetal circulation. Table III also shows that there was no significant difference in the indices of assessment of myocardial function i.e. fractional shortening and ejection fraction.
**TABLE IV: CLINICAL AND ECHOCARDIOGRAPHIC CHARACTERISTICS OF STUDY PATIENTS: UNIVARIATE ANALYSIS**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>hsPDA Present</th>
<th>hsPDA Absent</th>
<th>OR (95% C.I)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=30</td>
<td>n=126</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory Rate &gt;60</td>
<td>25 (83)</td>
<td>67 (53.2)</td>
<td>4.4 (1.56-12.2)</td>
<td>0.003</td>
</tr>
<tr>
<td>Lower Chest In drawing</td>
<td>20 (66.7)</td>
<td>43 (34.1)</td>
<td>3.86 (1.7-8.97)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heart rate &gt;160/Min</td>
<td>21 (70)</td>
<td>48 (38.1)</td>
<td>3.8 (1.6-8.9)</td>
<td>0.02</td>
</tr>
<tr>
<td>Bounding Peripheral Pulses</td>
<td>15 (50)</td>
<td>22 (17.5)</td>
<td>4.7 (2.0-11.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hyperactive Precordium</td>
<td>18 (60.0)</td>
<td>21 (16.7)</td>
<td>7.5 (3.1-17)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Murmur</td>
<td>14 (46.7)</td>
<td>18 (14.3)</td>
<td>5.3 (2.2-12.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>10 (33.3)</td>
<td>17 (13.5)</td>
<td>3.2 (1.3-8)</td>
<td>0.01</td>
</tr>
<tr>
<td>Congestive Cardiac failure</td>
<td>10 (33.3)</td>
<td>8 (6.3)</td>
<td>7.3(2.6-21)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Antenatal corticosteroid use</td>
<td>1 (3.3)</td>
<td>21 (16.7)</td>
<td>0.17 (0.02-1.3)</td>
<td>0.059</td>
</tr>
<tr>
<td>Phototherapy</td>
<td>11 (36.7)</td>
<td>23 (18.9)</td>
<td>2.5(1.1-5.9)</td>
<td>0.036</td>
</tr>
</tbody>
</table>

(*) *Shows the percentage of infants with the clinical sign.

Table IV shows that lower chest indrawing, bounding peripheral pulses, hyperactive precordium and presence of a murmur as signs which show significant association with a haemodynamically significant PDA. A murmur (systolic or continuous) was heard in 46.7% of infants with hsPDA.
Eleven infants with hsPDA (36.7%) were having phototherapy compared with 23 (18.9%) of infants without hsPDA. Infants undergoing phototherapy were more likely to have hsPDA compared to those not undergoing phototherapy ($X^2=4.4$, OR 2.5 95%CI (1.0-5.9) p<0.05. However on controlling for birth weight and gestational age in a multivariate analysis the effect was not statistically significant (p=0.058)

Twenty one infants (16.7%) without hsPDA had their mothers given antenatal corticosteroid for the purpose of enhancing lung maturation compared with 3.3% of those with hsPDA. The influence of this was not of statistical significance because of the small numbers involved.

Infants with congestive cardiac failure were more likely to have a haemodynamically significant PDA

**MULTIVARIATE ANALYSIS**

The significant clinical signs in the univariate model were entered into multiple logistic regression model while controlling for birth weight and gestational age. A logistic regression was used with variables added in a stepwise in a forward and backward regression. The factor which remained statistically significant in predicting the presence of a hsPDA was hyperactive precordium (OR 4.08 95%CI 1.1-15.6 p<0.05)
### TABLE V: PREDICTIVE VALUE, SENSITIVITY AND SPECIFICITY OF CLINICAL SIGNS FOR HSPDA

<table>
<thead>
<tr>
<th>Sign</th>
<th>Positive predictive value</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Tachypnea</td>
<td>25/92 (27)</td>
<td>25/30</td>
<td>59/126</td>
</tr>
<tr>
<td>Chest indrawing</td>
<td>20/63 (31.7)</td>
<td>20/30</td>
<td>83/126</td>
</tr>
<tr>
<td>Bounding peripheral pulses</td>
<td>15/37 (40.5)</td>
<td>15/30</td>
<td>104/126</td>
</tr>
<tr>
<td>Hyperactive precordium</td>
<td>18/39 (46.2)</td>
<td>18/30</td>
<td>105/126</td>
</tr>
<tr>
<td>Murmur(systolic or continuous)</td>
<td>14/32 (43.8)</td>
<td>14/30</td>
<td>108/126</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>10/27 (37)</td>
<td>10/30</td>
<td>109/126</td>
</tr>
</tbody>
</table>

Table V shows that the presence of tachypnea beyond day 3 has high sensitivity for hsPDA. Apart from the respiratory sign, hyperactive precordium shows sensitivity of 60% and a specificity of 83.3% for hsPDA. However in general, the clinical signs showed poor predictive values for hsPDA with the most predictive being hyperactive precordium (46%).

Among the study patients, 22 (14.1%) were suspected by the primary clinician to have PDA based on clinical signs. Of the patients suspected to have PDA, 10 were found to have hsPDA on echocardiography. This showed a positive predictive value of 33.3%. However despite the low positive predictive value, infants suspected to have PDA by the primary clinician were at least 4 times more likely to have hsPDA than those in whom PDA was not suspected (OR 4.75 95% C.I. 1.8-12.5 P=0.002)
STUDY LIMITATION

1. This was a selection bias attributed to admission policy. E.g. the category of infants over 2000g consisted mainly those who were sick unlike in the <2000g category whom both sick and stable were admitted. This could explain the apparent high prevalence of hsPDA in this category.

2. After stratification of the data by birth weight and gestational age, some of the strata were inadequately represented e.g. the extremely low birth weight infants. Thus conclusions that could be derived from a stratified analysis were limited.
DISCUSSION

The prevalence of a hemodynamically significant PDA beyond day 3 in low birth weight preterm infants at KNH was 19.2%. The prevalence in those with a birth weight below 2000g was 18.5%, which depicts a relatively high, compared with a previous study at the unit that demonstrated a prevalence of 8.9% in the same birth weight category. The previous study was based on the presence of murmurs suggestive of PDA.27 Although the prevalence of hsPDA has been reported to increase especially closely related to improved survival of very low birth weight and extremely low birth weight infants in other centers, the apparent high prevalence compared to the previous study at KNH may be related to the wider use of echocardiography as a diagnostic tool.

This study also showed a relatively high prevalence of hsPDA in the weight category above 2000g of 21.4%. This could be as a result of the admission criteria for the unit for those infants with birth weight above 2000g. Where as both stable and sick babies with birth weight below 2000g are admitted to the unit largely based on weight criteria, those infants above 2000g are admitted because of intercurrent illness. The role of the intercurrent illness especially those associated with hypoxia in the delayed ductal closure or reopening of the ductus is well established.15, 16 The commonest illnesses at the time of admission were respiratory distress syndrome (71.2%) and neonatal sepsis (28.8%).
However, most patients had multiple diagnoses at the time of admission to the unit and also at the time of enrollment into the study. RDS has been shown to have a predictive value of 78-83% for PDA in several studies, although this could not be substantiated in this study because of the varied timing of assessment of the infants. Some infants were assessed beyond the time when RDS has been shown to have maximum impact on the presence of hsPDA. Despite this, tachypnea and lower chest indrawing showed sensitivities of 83.3% and 66.7% respectively for hsPDA. Tachypnea OR, 4.4 (95%CI, 1.56-12.2, P=0.03) and lower chest indrawing OR 3.86 (95%CI, 1.7-897, P<0.001) demonstrated a significant association with presence of hsPDA. Tachypnoea beyond day 3 had the highest sensitivity for hsPDA and therefore could be used to guide patient selection for screening.

Another risk factor for PDA is the exposure to phototherapy. Rosenfield et al. in a study of preterm infants showed that phototherapy increased the risk for hsPDA and that the risk could be reduced by use of protective chest shielding. Eleven (36.7%) of patients with hsPDA were on phototherapy while 18.9% of those without hsPDA were undergoing phototherapy. Patients on phototherapy had at least a two fold increased risk of having hsPDA. (OR 2.5 95% C.I.1.1-25.9) p<0.036. However on multivariate analysis this was not of statistical significance (p=0.58). This study did not factor in the duration of exposure to phototherapy.
A history of antenatal corticosteroid has been shown in some studies to reduce the prevalence of hsPDA. Clyman et al in a study of the role of prenatal administration of betamethasone for prevention of PDA found that infants whose mothers had received antenatal corticosteroid for the purpose of enhancing fetal lung maturation had a lower incidence of PDA. In this study only 21(13.5%) infants had their mothers receive prenatal corticosteroid for this purpose. One infant (3.3%) of those with hsPDA as contrasted with 23(18.9%) of those without hsPDA had received prenatal corticosteroid therapy. However the reduction in risk for hsPDA was not of statistical significance. (p=0.059).

Fluid overload has been known to increase the prevalence of hsPDA. PDA has been shown to occur in fluid overload states. In this study there was no significant difference in the mean volume of fluid given to those with hsPDA compared to those without hsPDA.

The presence of anemia can also alter the presentation of patients with hsPDA. Some clinical signs of PDA mimic those of anemia especially the presence of a murmur and bounding pulses. In this study there was no significant difference in the mean hemoglobin concentration of patients with hsPDA and those without hsPDA.

In the analysis of clinical signs and their relationship to the presence of hsPDA, hyperactive precordium showed the highest association with the presence of hsPDA (OR 7.5 95%CI 3.1-17) p<0.05.
Kupfershmidt et al demonstrated a study of preterm infants with symptomatic PDA that hyperactive precordium is the most predictive sign for hsPDA. However, its positive predictive value was too low (46.2%) to be of clinical importance.

The presence of a murmur was demonstrated in 46.7% of patients with hsPDA. It demonstrated a significant association with the presence of hsPDA OR 5.3 95%CI. 2.2-12.65) p < 0.05. The presence of a murmur showed a high specificity for the presence of hsPDA. A systolic sternal border murmur or continuous murmur is however not always predictive of the presence of a PDA or hsPDA.

In this study, some clinical signs showed high specificity but low sensitivity and low positive predictive values for hsPDA. This means that although PDA is common in low birth weight preterm infants, reliance on clinical signs alone can lead to under diagnosis of PDA. In most centers in the developed countries, low birth weight preterm infants undergo routine timed echocardiography to determine the presence of a significant PDA. At KNH mostly those infants who have clinical signs suggestive of PDA or in whom a congenital heart disease is suspected are subsequently evaluated echocardiographically. This method of patient selection based on clinical signs leads to under diagnosis. Among the study patients, 22(14.1%) were suspected by the primary clinician to have PDA based on clinical signs. Of the patients suspected to have PDA, 10 were found to have hsPDA on echocardiography. This showed a
positive predictive value of only 33.3% and hence a significant number of patients with hsPDA were missed on clinical evaluation. In addition to this, delayed diagnosis occurs as patients are evaluated when they have more overt clinical signs and this occurs mostly late in the course of the disease. Delayed diagnosis has its undesirable effects in that patients manifest with complications of PDA. This study showed that 10 (33.3%) of patients with hsPDA had congestive heart failure at the time of diagnosis of the condition. The presence of the congestive cardiac failure is a late event in the clinical course of hsPDA and hence the need to aim for early diagnosis and treatment.
1. HsPDA is a common in low birth weight preterm infants with a prevalence of 19.2% in those 3 days and above.

2. The presence of tachypnea beyond day 3 gave the highest sensitivity for hsPDA and therefore can be used to direct screening.

3. The presence of certain clinical signs showed high specificity for hsPDA e.g. presence of a murmur (85.7%), hyperactive precordium (83.3%) and bounding pulses (82.5%). These are useful as indicators of hsPDA when present, but reliance on these signs alone leads to underdiagnosis.
RECOMMENDATION

Haemodynamically significant PDA is a highly prevalent condition in low birth weight preterm infants and steps to actively screen for it will enhance its diagnosis and management. With limited resources, a better yield for hsPDA can be obtained by screening all infants with the most sensitive sign for hsPDA i.e. tachypnea beyond day 3 of life. Improved availability and utilization of echocardiography in the newborn unit will improve the diagnosis and follow up of patients with hsPDA or those at risk of developing hsPDA.
APPENDIX 1

1. Patient's Particulars
   
a) Hospital No..............................................
b) Study No...............................................c) Sex....................................................
d) Birth weight ..........................................e) Date of birth ........................................
f) Age ............ days ...............................g) Current weight ........................................
h) Height................................. Cm          i) Surface area................................. $M^2$

2. Antenatal and natal History
   
a) Gestational age at delivery by dates........... Weeks
      By new Ballard score........... Weeks
   
   b) Maternal antenatal illness

      Yes □
      No □
      Diagnosis..............................................

   c) History of antenatal corticosteroid use

      Yes □
      No □

   d) Mode of delivery

      i. Spontaneous vertex delivery □
      ii. Breech delivery □
      iii. Caesarian section □

   e) If caesarian section, what was the reason for caesarian section?

      ........................................................................................................

      ........................................................................................................

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3. Diagnosis at admission to newborn unit
   i. Respiratory distress syndrome
   ii. Neonatal sepsis
   iii. Birth asphyxia
   iv. Neonatal jaundice
   v. Others (specify)

**PHYSICAL EXAMINATION**

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>Present</th>
<th>Absent</th>
</tr>
</thead>
<tbody>
<tr>
<td>4. Pallor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Edema</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. cyanosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Jaundice</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. Respiratory rate &gt;60</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9. Lower chest indrawing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10. Apneic episode in last 24 hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11. Bradycardia &lt; 60 /min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12. Tachycardia &gt;160/ min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13. Bounding peripheral /pulses</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14. Wide pulse pressure &gt;25 mmHg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15. Hyperactive precordium</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16. Gallop rhythm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17. Rales</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18. (a) Murmur</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(b) Type of murmur if present</td>
<td></td>
<td></td>
</tr>
<tr>
<td>i. Location</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ii. Systolic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>iii. Diastolic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>iv. Continuous</td>
<td></td>
<td></td>
</tr>
<tr>
<td>19. Liver span</td>
<td></td>
<td>cm</td>
</tr>
</tbody>
</table>

54
Below sub costal margin ............cm

20. Hepatomegaly present  □  absent □

21. Congestive cardiac failure present □  absent □

22. Temperature .................................................°c

23. Working diagnosis
   a) Respiratory distress syndrome  □
   b) Neonatal sepsis  □
   c) Neonatal jaundice  □
   d) Anemia  □
   e) Others (specify)

24. PDA clinically suspected by primary clinician  Yes □   No □

25. Investigations done
   a) Hemoglobin level............g/dl  □
   b) CXR
      i. Lung fields..............................................................
      ii. Cardiothoracic ratio..............................................
   c) Blood culture ......................................................
   d) Others

26. Site of care
   a) Incubator care □
   b) Cot care  □

27. Mode of feeding
   a) Predominantly />50% oral  □
   b) Predominantly parenteral  □
   c) Volume of feed in previous 24 hours
      i. Oral .......................................................... ml/kg
      ii. Parenteral ..................................................... ml/kg

28. Is the patient on phototherapy?
   Yes □   No □
APPENDIX2

<table>
<thead>
<tr>
<th>Neuromuscular Maturity</th>
<th>1</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Posture</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Square Window</strong></td>
<td></td>
<td></td>
<td>90°</td>
<td>90°</td>
<td>60°</td>
<td>45°</td>
<td>30°</td>
</tr>
<tr>
<td>(wrist)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Arm Recoil</strong></td>
<td></td>
<td></td>
<td>180°</td>
<td>140°-180°</td>
<td>110°-140°</td>
<td>90°-110°</td>
<td>90°</td>
</tr>
<tr>
<td><strong>Popliteal Angle</strong></td>
<td></td>
<td></td>
<td>180°</td>
<td>160°</td>
<td>140°</td>
<td>120°</td>
<td>100°</td>
</tr>
<tr>
<td><strong>Scarf Sign</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Heel to Ear</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Physical Maturity</th>
<th>sticky</th>
<th>gelatinous</th>
<th>smooth</th>
<th>superficial</th>
<th>cracking</th>
<th>leathery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>fragile</td>
<td>red, translucent</td>
<td>pink, visible veins</td>
<td>peeling &amp; rash</td>
<td>pale areas</td>
<td>cracked</td>
</tr>
<tr>
<td></td>
<td>transparent</td>
<td></td>
<td></td>
<td>few veins</td>
<td>rare veins</td>
<td>no vessels</td>
</tr>
<tr>
<td>Lanugo</td>
<td>none</td>
<td>sparse</td>
<td>abundant</td>
<td>thinning</td>
<td>bald</td>
<td>mostly</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>areas</td>
<td></td>
</tr>
<tr>
<td>Plantar Surface</td>
<td>heel-toe</td>
<td>40-50 mm</td>
<td>40 mm</td>
<td>&gt;50 mm</td>
<td>&lt;40 mm</td>
<td>creases</td>
</tr>
<tr>
<td></td>
<td>40-50 mm</td>
<td>40 mm</td>
<td>40 mm</td>
<td>no crease</td>
<td>no crease</td>
<td>ant 2/3</td>
</tr>
<tr>
<td>Breast</td>
<td>imperceptible</td>
<td>barely perceptible</td>
<td>flat areola</td>
<td>no bud</td>
<td>stipped</td>
<td>raised</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>areola</td>
<td>areola</td>
</tr>
<tr>
<td>Eye/Ear</td>
<td>lids fused</td>
<td>lids open</td>
<td>sl. curved</td>
<td>well-curved</td>
<td>formed</td>
<td>thick</td>
</tr>
<tr>
<td></td>
<td>loosely</td>
<td>pinna flat</td>
<td>pinna, soft</td>
<td>pinna, soft</td>
<td>&amp; firm</td>
<td></td>
</tr>
<tr>
<td></td>
<td>40 mm</td>
<td>stays folded</td>
<td>slow recoil</td>
<td>slow recoil</td>
<td>instant</td>
<td></td>
</tr>
<tr>
<td>Genitals male</td>
<td>scrotum</td>
<td>empty</td>
<td>tests in</td>
<td>tests</td>
<td>tests</td>
<td>tests</td>
</tr>
<tr>
<td></td>
<td>smooth</td>
<td></td>
<td>upper canal</td>
<td>descending</td>
<td>down</td>
<td>pendulous</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>rare rugae</td>
<td>few rugae</td>
<td>good</td>
<td>deep rugae</td>
</tr>
<tr>
<td>Genitals female</td>
<td>clitoris prominent</td>
<td></td>
<td>prominent</td>
<td>prominent</td>
<td>majora</td>
<td>majora</td>
</tr>
<tr>
<td></td>
<td>labia flat</td>
<td></td>
<td>clitoris small</td>
<td>clitoris large</td>
<td>&amp; minora</td>
<td>&amp; minora</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>labia minora</td>
<td>minora</td>
<td>equally</td>
<td>equally</td>
</tr>
</tbody>
</table>

New Ballard score sheet for assessment of gestational age 47
### APPENDIX 3

**STUDY OF PREVALENCE AND CLINICAL CORRELATES OF HAEMODYNAMICALLY SIGNIFICANT PATENT DUCTUS ARTERIOSUS: ECHOCARDIOGRAPHY REPORT.**

<table>
<thead>
<tr>
<th>IP NO.</th>
<th>SEX</th>
<th>AGE</th>
<th>DATE</th>
<th>Study No.</th>
<th>HEIGHT (cm)</th>
<th>WEIGHT</th>
<th>BSA</th>
</tr>
</thead>
</table>

#### A) M-MODE

<table>
<thead>
<tr>
<th>LVDDd</th>
<th>LVDSs</th>
<th>RVDDd</th>
<th>EF (%)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>LA</th>
<th>AO</th>
<th>LA:AO ratio</th>
<th>FS (%)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>LVPWs</th>
<th>IVSs</th>
<th>CO</th>
<th>HR</th>
</tr>
</thead>
</table>

#### B) 2DIMENSIONAL AND COLOR FLOW MAP

- PDA present [ ]
- absent [ ]

#### C) Shunt quantification

1. **PDA size**
   - Suprasternal: mm
   - Parasternal short axis: mm

2. **Average PDA Dimension**: mm

3. **DOPPLER**: PDA
   - Diastolic: 
   - Systolic: 

4. **Estimated pulmonary artery pressure**: mmHg

#### E) Other

- Findings: 

- Echocardiography done by: 
- Investigator: 

---

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APPENDIX 4

Rowe et al guidelines for diagnosis of heart failure in Newborns (44).

A: Suggestive of heart failure
Any 3 of the following

Cardiomegaly (Cardiothoracic ratio >0.6)
Tachycardia (>150/min)
Tachypnea (>60 per min)
Wet lungs

B: Diagnostic of heart failure.
Criteria A above plus any of the following

Hepatomegaly (>3 cm)
Gallop rhythm
Frank pulmonary edema

C. Severe heart failure
Vascular collapse
BIBLIOGRAPHY


43. Leung MP, Cheug DLC, Lo RN. The management of symptomatic neonates using combined cross-sectional echocardiography and pulsed
Doppler flow study as the definitive investigations. Int J Cardiol 1989; 24:41-46.


