Incidence and risk factors associated with the patency of ductus arteriosus in preterm infants with respiratory distress syndrome in Kuwait

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ABSTRACT

Objectives: Patent ductus arteriosus (PDA) is considered to be an important cause of morbidity and mortality among preterm infants. The aim of this study is to determine the incidence of PDA in ventilated preterm infants with respiratory distress syndrome (RDS) and to evaluate the role of some antenatal risk factors on its occurrence in our population.

Methods: The case records of the preterm infants of <34 weeks gestational age, who were ventilated for RDS at the neonatal intensive care unit of Maternity Hospital, Safat, Kuwait, between March 1998 and February 1999, were reviewed. Diagnosis of PDA was based on echocardiographic findings. The association between the risk factors chosen and the PDA was also evaluated.

Results: A total of 101 infants whose gestational ages ranged between 25-33 weeks, and birth weights between 685-1580 grams were included. Fifty-four had a significant PDA (53.4%). Maternal diabetes and antepartum hemorrhage (APH), birth weights, gestational ages, multiplicity and gender of the infants were found to be related to the incidence of PDA.

Conclusion: The incidence of PDA in our ventilated preterm infants with RDS is similar to those reported from other neonatal units outside Kuwait. There are some factors that may identify babies, who are prone to develop PDA, which need to be confirmed by further prospective studies using a larger population.

Saudi Med J 2003; Vol. 24 (9): 982-985

The clinical recognition that preterm infants especially those with respiratory distress syndrome (RDS) are at risk of developing patent ductus arteriosus (PDA) is well established.[1,2] The presence of a significant left to right shunt through a PDA is reported to occur in 11-69% of very low birth weights (VLBW) infants.[3-5] Patent ductus arteriosus is considered to be an important cause of morbidity and mortality among this population.[6] Some complications in preterm infants are recognized more in the presence of PDA such as chronic lung disease (CLD) and necrotizing enterocolitis (NEC) and these were significantly reduced when early treatment for the PDA was introduced.[7] The differences in the diagnostic criteria (symptomatic versus

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Received 13th April 2003. Accepted for publication in final form 2nd June 2003.

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asymptomatic PDA), and the therapeutic intervention; as well as the differences in the selected population may all add to the varying range of incidence reported in the literature.[8,9] As there were no previously reported studies in Kuwait on the incidence of PDA, this study attempted to fill the gap in finding the incidence of PDA early in life in ventilated preterm infants <34 weeks gestation and to evaluate some antenatal factors that are associated with the occurrence of PDA.

Methods. A retrospective review of the data files of preterm infants <34 weeks admitted to the neonatal intensive care unit (NICU) of Maternity Hospital, Kuwait and ventilated for RDS between March 1998 and February 1999, was undertaken. Files were examined for the presence or absence of PDA in the selected population. Infants included were the inborn who had moderate to severe RDS (with documented oxygen [O_2] requirements of >50% to maintain normal arterial oxygen tension [PO_2] and a chest x-ray appearance consistent with RDS), and were admitted after birth to NICU, ventilated, and received surfactant therapy. Infants with a major congenital malformations and those who died in the first 3 days of life were excluded. According to the protocol applied in the unit, the diagnosis of PDA was made by a comprehensive 2-dimensional, cross-sectional and M-mode echocardiography with pulsed-wave and color flow Doppler (Apogee CX, ATL, 7.5 MHZ probe) in infants who had a clinical evidence of PDA (tachycardia, hyperdynamic precordium, or bounding pulses with or without a murmur). The echocardiographic criteria, which was used to label the PDA as significant were: ductal size ≥2 mm and left atrial diameter to aortic root ratio ≥1.5 together with left ventricular enlargement. All the echocardiographic examinations were carried out by a single cardiologist within the first week of life (range of 3-7 days of life). Information on maternal, intrapartum and neonatal factors were extracted from the mothers' and infants' medical records. Maternal factors such as diabetes, pregnancy induced hypertension (PIH), prolonged rupture of membranes (PROM), antepartum hemorrhage (APH), and antenatal steroids were studied. Infant factors that were studied included fetal distress and the mode of delivery (cesarean section [CS] versus vaginal delivery), multiplicity, gender, gestational age, weight and apgar score at 5 minutes.

A total of 101 consecutive infants were included in this study. These infants were divided into 2 groups; those with and without significant PDA. The medical and ventilatory management for all the infants are strictly according to the protocol applied in the unit. Statistical analyses were conducted to examine the association between PDA and the risk factors using SPSS software program. Results were estimated from Z-normal test for the differences between proportions, student t-test to compare the means of 2 quantitative variables, and the logistic regression analysis to find the independent risk factors for the development of PDA.

Results. Out of the 101 infants studied, 54 (53.4%) had significant PDA while the rest (46.6%) had no significant PDA according to the study criteria. In **Table 1** maternal factors studied in relation to PDA revealed a higher percentage of mothers with diabetes in the PDA group (20.3% versus 4.2%, $p<0.05$). Antepartum hemorrhage was also significantly higher among the mothers in the PDA group (18.5% versus 4.2%, $p<0.05$). However, the incidence of PDA was not found to be significantly associated with PIH or PROM. Moreover, the antenatal steroids did not show to affect significantly the incidence of PDA. Among the neonatal variables studied, gestational age, birth weight, gender and multiplicity were found to be significantly related to PDA incidence ($p<0.001$, $p<0.0001$, $p<0.05$, $p<0.05$). The gestational age and birth weight were lower in those with PDA, and the incidence was higher among the lower gestational age groups (25-29 weeks) (**Table 1**). As the gestational age increases the risk of having PDA appears to decrease (**Figure 1**). Similar pattern also existed for the birth weight. Incidence of PDA was higher among infants whose weights were <1000 grams (**Figure 2**). Male infants appeared more prone to develop PDA compared to female counterparts. Twenty-six percent of the infants with PDA were the result of multiple pregnancy, while only 8.5% were the result of multiple births among the non-PDA group. Apgar scores at 5 minutes and the mode of delivery (CS versus vaginal delivery) were not found to affect the incidence of PDA. Fetal distress was noticed in 4 of the enrolled infants and these belonged to the PDA group. A further multiple logistic regression analysis was carried out to identify the most significant factors related to PDA status of the infants. Multiple births (odds ratio [OR] was 3.8, confidence intervals [CI] was 1.5-12.4, $p<0.05$), diabetes in the mothers (OR = 6.3, CI = 1.28-27.5, $p<0.05$), and male gender (OR = 2.5, CI 1.2-5.6, $p<0.05$) were selected to be the most significant factors associated with PDA.

Discussion. Our study revealed that the incidence of PDA in the ventilated preterm infants with RDS in our department was found to be 53.4%. Using varying diagnostic criteria, earlier previous studies estimated the incidence of PDA in preterm infants with respiratory distress to range from 15-85% in infants <1800g.[9] However, the incidence between the ventilated and the unventilated infants was found to be different. The incidence of PDA in ventilator dependent infants surviving ≥3 days was 78% at 24-25 weeks, 45% at 26-27 weeks, 40% at 28-29 weeks, 38% at 30-31 weeks, 17% at 32-33 weeks and 6% at 34-36 weeks.[10] By any means PDA incidence in our hospital is more to the higher side compared with the other reported studies. However, this could be due to the population chosen, which included only the preterm infants <34 weeks who had lower birth weights, moderate to severe RDS, ventilated and received surfactant therapy. Several attempts have been made to determine infants at risk of

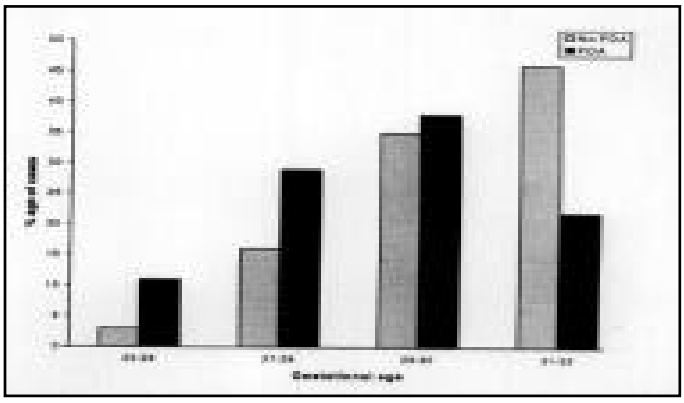

Figure 1 - Gestational age in relation to the patent ductus arteriosus (PDA) in preterm infants.

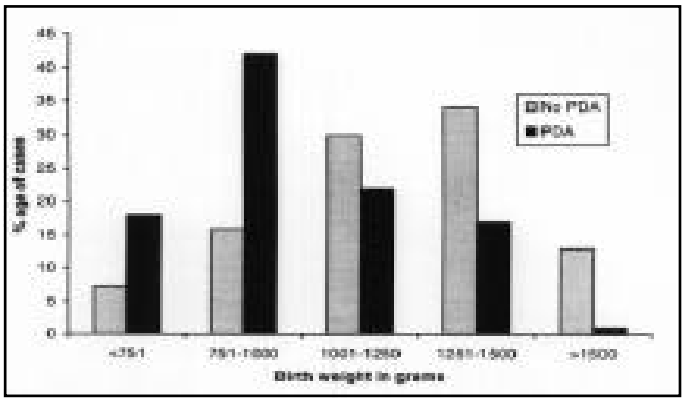

Figure 2 - Birth weight in relation to the patent ductus arteriosus (PDA) in preterm infants.

Table 1 - Association between patent ductus arteriosus (PDA) and maternal and neonatal variables.

Variables	PDA (N=54) n (%)	No PDA (N=47) n (%)	p-value
Maternal variables			
PROM*	13 (24)	10 (21.2)	NS
APH†	10 (18.5)	2 (4.2)	< 0.05††
PIH‡	6 (11)	9 (19)	NS
Diabetes mellitus§	11 (20.3)	2 (4.2)	<0.05††
Antenatal steroids	25 (46.2)	28 (59.5)	NS
Neonatal variables			
Sex			
Female	20 (37)	28 (60)	<0.05‡
Male	34 (63)	19 (40)	
Gestational age			
25-29 weeks	36 (67)	13 (28)	<0.001‡
30-33 weeks	18 (33)	34 (72)	
Mean+SD	29.2 ± 1.9	30.7 ± 2.4	<0.001§
Birth weight	959 ± 351	1250 ± 361	<0.0001§
Apgar score at 5 minutes	6.8 ± 1.7	7.3 ± 1.7	NS
Delivery mode (CS/VD)	31/54 (57)	26/47 (55)	NS
Multiple births	14 (26)	4 (8.5)	<0.05††
Fetal distress	4 (7.4)	-	-

*cesarean section (CS), †vaginal delivery (VD), ‡Chi square, §Student t-test, ††z-test of proportion, NS - not significant, PROM - prolonged rupture of membranes, APH - antepartum hemorrhage, PIH - pregnancy induced hypertension

developing PDA.[11,12] Our findings supported previous reports of an inverse relationship between the gestational age and the birth weight with the occurrence of the PDA.[9,13] The incidence of PDA has also been reported to be lower in infants whose mothers had received antenatal corticosteroid therapy.[14,15] Our study could not establish a significant statistical association between the incidence of PDA and antenatal steroids, and this was probably due to the small sample size .

In our study, maternal diabetes was found to be significantly associated with PDA. This was proved by both a univariate and a multiple regression analysis. Similar association was reported by Seppanen, et al.[16] This association may be related to a worse pulmonary disease in these infants due to their delayed pulmonary maturation; or it may be due to the myocardial hypertrophy, which is usually present in infants of diabetic mothers, as this may disturb the postnatal adaptation of the pulmonary circulation especially when it happens in the preterm infants. A higher incidence of PDA was noticed with APH, and the 4 cases of fetal distress were exclusively within the PDA infants. The mechanism of this association can be explained by the hypoxia that may cause delayed closure of the ductus arteriosus, as it is reported that constriction of the muscular wall of the ductus is usually initiated by an increase in the arterial oxygenation after birth.[17] Our study showed a relatively higher incidence of PDA with multiple pregnancy. Among infants with PDA, 40 were singletons, 13 were parts of twins and one was part of triplet, while among the non-PDA group; 43 were singletons and 4 were parts of twins. The mechanism can be explained by the increased risk of premature delivery with multiple pregnancy, which in turn can predispose these infants to an element of perinatal asphyxia, and both prematurity and asphyxia can increase the incidence of PDA.[17] To our knowledge the relationship between multiple pregnancy and PDA was not published previously. In this study, we also found a higher percentage of mothers with PIH in the non-PDA group. Although statistically not significant, it supported what was published by Shah et al,[18] that PDA occurred less frequently in preterm infants of hypertensive mothers. This was explained by the lower incidence of RDS in these infants, which could be the result of accelerated maturation of the lungs in such chronically, stressed infants.

In conclusion, considering the serious sequelae of PDA in the high-risk VLBW infants, it is apparent that anticipation and early treatment of PDA are paramount in this group, given the high incident rate. Therefore, we recommend a larger prospective clinical trial to investigate both the risk factors and the strategies for management in this group of patients.

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