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PATENT DUCTUS ARTERIOSUS;
ASSOCIATION WITH DIFFERENT RISK FACTORS

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ABSTRACT... Background: Patent Ductus Arteriosus (PDA) is a congenital cardiac disease of children. Lot of work has been done to evaluate the usefulness of management procedure including medical management and surgery but there is no evidence to evaluate the risk factors associated with PDA. Aim: To find out the association of risk factors leading to patent ductus arteriosus in children. **Method:** A case control study was conducted on 240 children, out of which 120 were cases and 120 were controls. Children of 1-15 years of either gender were included in the study through Simple Random sampling technique. Parents were called for interview and history of risk factors leading to PDA were asked and noted on questionnaire. Data was entered and analyzed through the computer software, SPSS version 21. **Results:** In this study, we included 240 children with the mean age of 4.86±4.01 years. There were 88 (37%) males while 152 (63%) were females. The male-to-female ratio was 1:1.7. The mean height of children was 3.52±1.18 feet and the mean weight of children was 24.98±11.34kg. Through logistic regression, it was observed that family history, over the counter drugs or antibiotic use during pregnancy, Down's syndrome and preterm birth were significantly effecting the occurrence of PDA ($P<0.05$), while female gender, smoking status of father and infection during pregnancy including rubella become insignificant ($P>0.05$). In logistic regression, it was observed that family history, over the counter drugs or antibiotic use during pregnancy, Down's syndrome and preterm birth were significantly affecting the occurrence of PDA ($P<0.05$). **Conclusion:** Female gender, preterm birth, infection during pregnancy and use of over the counter drugs in pregnancy, female's exposure to smoking and multiple drugs and low birth weight are significant risk factors associated with PDA.

Key words: Patent Ductus Arteriosus, gender, Down's syndrome, rubella, preterm birth, low birth weight

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INTRODUCTION

Before birth of a baby, the blood of fetus does not require to pass through the lungs to get oxygenated. So, the ductus arteriosus is an open passage which allows the blood to skip the tour to lungs. But, after birth, the blood necessitate oxygen in lungs and this opening is thought to close. If ductus arteriosus remains open or patent, the blood may skip this obligatory step of circulation. This opening is called patent ductus arteriosus (PDA).[1]

PDA is a congenital disorder in the heart wherein a neonate's ductus arteriosus fails to close after birth. Early symptoms are uncommon, but in the first year of life include increased work of breathing and poor weight gain.[2] PDA represents 5-10% of all congenital heart lesions.[3] PDA is the existence of a hole between the descending aorta and the left pulmonary artery. The ductus usually close soon after birth. But if not close within 10 days of birth, then it is considered to be abnormal.[4]

PDA is common congenital heart disease. It

occurs more commonly in preterm neonates, in about 8 of 1000 births and is likely to be as high as 1 in 500. But, it also occurs in full-term infants (approx. 1 in 2000 births).[2,5,6] A survey conducted in KPK in 2002, frequency of PDA in newborns was 9.7%.[7] But later on, in 2011, the frequency was increased to 12.8% in Peshawar, KPK.[8]

In a study conducted in 2013 reported some factors leading to PDA. In this study it was reported that 17.8% patients inherited the disease from first relatives and 43.4% mothers had infectious problems in pregnancy, 42.6% mothers took over the counter antibiotics during pregnancy (without prescription of physician), 4.5% children had Down syndrome and 56.61% children had preterm birth. It was concluded that being female, preterm delivery, infection in pregnancy, exposure to smoking of mother and antibiotics, low birth weight may be significant risk factors of PDA.[9]

Females have 2-3times more chance of PDA as compared to males. Although one investigation reported 53% cases were males in all PDA patients.[10-12]

PDA is more common in preterm delivered babies and is less likely to occur in full term babies (>37 weeks of gestation). Incidence is 20% for preterm infants >32 weeks' but 60% in those <28 weeks' gestation. About 30% of low birth weight neonates (<2500 g) grow PDA.[13]

The incidence of PDA is inversely related to gestational age and birth weight. A hemodynamically significant thrust because of PDA has been described in 40% of neonates <1000grams and 20% of neonates weighed 1000-1500grams.[14]

PDA risk increases with maternal diabetes.[10,15-17] It is also considered that PDA is not associated with maternal ampicillin use during pregnancy.[18] While one study testified increased risk of PDA with maternal direct or indirect smoking, but other studies could not find such association.[19-21]

Significance of study

Medicine or pharmacological closure by indomethacin is customary if symptoms of PDA are not controlled adequately with fluid restriction and diuretics. Its use, however, requires a comprehensive clinical assessment of all the vital perinatal factors and a vigilant monitoring of the sick infant. The decision to use pharmacological versus surgical treatment or both should be individualized based on evidence-based research and clinician's own experience. Surgical ligation remains the primary mode of therapy in cases of pharmacological treatment failure or recurrence.

In Pakistan there is no specific study or research or article related to this topic. I want to aware the people particularly females to be careful during pregnancy and should be conscious about their health during pregnancy to prevent their children from such disease. Because mostly cases are related to the problems with females during pregnancy such as rubella; a risk factor. Therefore, we conducted this study to find the association of risk factors of PDA in local setting.

Objective

1. To assess the association of different risk factors of patent ductus arteriosus in children
2. To find the effect of multiple risk factors with PDA in children

Hypothesis

There is significant association of different risk factors with patent ductus arteriosus in children. There is significant effect of multiple risk factors with patent ductus arteriosus in children

MATERIALS AND METHODS

This Case Control study was conducted in Punjab Institute of Cardiology, Lahore to included cases of PDA and local Community to take controls (children without PDA or any other congenital heart disease). Sample size was calculated by using WHO software for sample size calculation. Sample size of 211 cases was calculated with 95% confidence level, 6% margin of error and taking percentage of PDA i.e. 9.7% among local population. In 211 samples, 10% of 211 =21

cases in original sample was added to control missing data or rectify sampling error. So total sample was 232, which was then rounded as 240. By taking ratio of 1:1 i.e. case and control, sample size was divided in two equal groups; 120 cases and 120 matched controls were included.

The children in both groups were included in the study through Simple Random sampling. Children of age 1-15 years of either gender were included. Case group: Children with PDA. Control group: Children without PDA or any other heart disease (normal children). Controls were selected and interviewed from community.

STUDY VARIABLES

a) **Dependent variable:** Children with PDA (cases) or Children without PDA (controls).
b) **Independent variables:** Gender, Family history, Father Smoker, Infection during pregnancy including rubella, overt the counter drugs use during pregnancy, Down syndrome, Preterm birth.

Data collection Procedure

After taking approval from hospital and permission from University authorities, 240 children fulfilling selection criteria were enrolled in the study. 120 cases of PDA were recruited through simple random sampling method while 120 control (normal children) were included from houses from different areas of Lahore. Informed consent were taken from parents of each child and were ensured about the confidentiality of their information used for research purpose only. Then their demographic details including name, age, gender, height, weight, area of residence and socioeconomic status were noted. Then parents of the children were interviewed by researcher. Parents of case group were presented with their children for follow-up in the hospital and they were interviewed in the hospital. Parents of control group were interviewed at their home places. All parents were interviewed in Urdu and separate questionnaire was used for each individual. Parents were asked about the family history of PDA among parents or grandparents for presence of PDA, smoking status of father, infection during pregnancy while she borne effected child and female took over the counter drugs particularly antibiotics during pregnancy (without physicians prescription) for infection in that pregnancy and gestational age at time of birth (either preterm birth or child was born at term and child was examined for presence or absence of Down's syndrome.

Data Collection Tool

Data was collected using structured and pretested questionnaire that contains demographic information, clinical examination and risk factors.

Data Analysis Plan

Data was entered and analyzed through the computer software, SPSS version 21. Quantitative variables like age, height and weight were calculated as mean and standard deviation. Categorical variables like residential area, socioeconomic status, Gender, Family history, Father smoker, Infection during pregnancy including rubella, over the counter drugs particularly antibiotics during pregnancy, Down syndrome, Preterm birth were calculated as frequency and percentage. Odds ratio for each factor were calculated to measure the association between risk factors and study group. OR>1 was considered as risk of association between risk factor and study group. Logistic regression was applied to measure the association of multiple factors on dependent variable (case/control). Beta values, confidence intervals of beta and significance of beta for each factor were calculated through logistic regression. P-value ≤ 0.05 was considered as significant.

Logistic regression Model

$Y = \text{Constant} + \exp(\beta1 * \text{gender} + \beta2 * \text{Family history} + \beta3 * \text{Father smoker} + \beta4 * \text{Infection during pregnancy including rubella} + \beta5 * \text{Antibiotics use during pregnancy} + \beta6 * \text{Down syndrome} + \beta7 * \text{Preterm birth}) / 1 + \exp(\beta1 * \text{gender} + \beta2 * \text{Family history} + \beta3 * \text{Father smoker} + \beta4 * \text{Infection during pregnancy including rubella} + \beta5 * \text{Antibiotics use during pregnancy} + \beta6 * \text{Down syndrome} + \beta7 * \text{Preterm birth})$

Ethical Consideration

As the study involves human subjects. The data was collected by taking ethical issues in consideration. Data was collected after the permission of high authorities of Punjab Institute of Cardiology, Lahore. Data was collected after taking informed consent from parents at the time of enrolment.

RESULTS

In this study, we included 240 children with the mean age of 4.86±4.01 years (range 1-15 years). There were 148(61.7%) children of age 1-4 years, 49(20.4%) children were of age 5-8 years, 21(8.8%) children were of age 9-12 years and 22(9.2%) children were of age 13-16 years. There were 88(37%) males while 152(63%) were females. The male-to-female ratio was 1:1.7. The mean height of children was 3.52±1.18 feet and the mean weight of children was 24.98±11.34kg. There were 174(72.5%) children who belonged to urban area while 66(27.5%) children belonged to rural areas.

There were 52(21.7%) families of children had low socioeconomic status, 138(57.5%) families of children belonged to middle socioeconomic status and 50(20.8%) families of children belonged to high socioeconomic status. Among cases, there were 50(41.7%) male children and 70(58.3%) female children. Among controls, there were 38(31.7%) male children and 82(68.3%) female children. The odds ratio was calculated as 1.541 (95% CI; 0.908, 2.616), showing that if gender of child is female at time of birth, there will be 1.5 times more chances of neonate to born with PDA. The difference was insignificant (P>0.05), but the female gender is found to be associated with PDA. Among cases, there were 26(21.7%) children had positive family history while among controls, there were 17(14.2%) children had positive family history of PDA. In most of the cases, grandparents had history of PDA. The odds ratio was calculated as 1.676 (95% CI; 0.856, 3.282), showing that if family history of child is positive, there will be 1.7 times more chances of neonate to born with PDA. The difference was insignificant (P>0.05), but the positive family history of PDA is found to be associated with PDA.

Among cases, there were 82 (68.3%) children whose fathers were smoker while among controls, there were 70(58.3%) children whose father were smoker. The odds ratio was calculated as 1.541 (95% CI; 0.908, 2.616), showing that if father is smoker and mother is a passive smoker, there will be 1.5 times more chances of neonate to born with PDA. The difference was insignificant (P>0.05), but the smoking status of father is found to be associated with PDA. Among cases, mothers of 96(80%) children had history of severe infection during pregnancy of this particular child while among controls, mothers of 9(7.5%) children had history of severe infection during pregnancy of this particular child. The odds ratio was calculated as 49.333 (95% CI; 21.873, 111.267), showing that if mother would have severe infection including rubella during pregnancy, there will be 49 times more chances of neonate to born with PDA. The difference was significant (P<0.05), and infection during pregnancy is found to be associated with PDA.

Among cases, mothers of 95 (79.2%) children reported that they used over the counter antibiotics or drugs for management of severe infection during pregnancy of this particular child while among controls, mothers of 8(6.7%) children reported that they used over the counter antibiotics or drugs for management of severe infection during pregnancy of this particular child. The odds ratio was calculated as 53.200 (95% CI; 22.926, 123.449), showing that if mother would use over the counter drugs or antibiotics to resolve their issue of infection or other problem during pregnancy, there will be 53 times more chances of neonate to born with PDA. The difference was significant (P<0.05), and use of medication without prescription of physician is found to be associated with PDA.

Among cases, 10(8.3%) children had Down's syndrome while among controls, 1(0.8%) children had Down's syndrome. The odds ratio was calculated as 10.818 (95% CI; 1.362, 85.896), showing that child had Down's syndrome, there

will be 10.8 times more chances of neonate to born with PDA. The difference was significant (P<0.05), and Down's syndrome is found to be associated with PDA. Among cases, 70(58.3%) children had preterm birth while among controls, 65(54.2%) children had preterm birth. The odds ratio was calculated as 1.185 (95% CI; 0.711, 1.974), showing that child who had preterm birth, there will be 1.2 times more chances of neonate to born with PDA. The difference was insignificant (P>0.05), but preterm birth is found to be associated with PDA.

In this study, logistic regression was applied. Cox & Snell R^2 was calculated as 0.569 while Nagelkerke R^2 was calculated as 0.759. These are pseudo values of R^2, can approximate R^2 showing that data is 75.9% good and model can be build. But the values of Cox & Snell and Nagelkerke R^2 are pseudo values; we cannot totally rely on these values as R^2 is based on linear regression (quantitative entities). So we moved to classification table and value of Overall Percentage in classification table shows the significance of data. In this study, the Overall Percentage was calculated as 91.7%, showing that 91.7% model is accepted in regression equation.

Logistic regression is applied to see the effect of multiple risk factors on occurrence of PDA in children as a congenital problem, it was observed that family history, over the counter drugs or antibiotic use during pregnancy, Down's syndrome and preterm birth were significantly effecting the occurrence of PDA (P<0.05), while female gender, smoking status of father and infection during pregnancy including rubella become insignificant (P>0.05).

n	120
Age (Years)	4.86±4.01
Height (feet)	3.52±1.18
Weight (kg)	24.98±11.34
Residential area Urban / rural	174 / 66

Table-I. Baseline characteristics of children

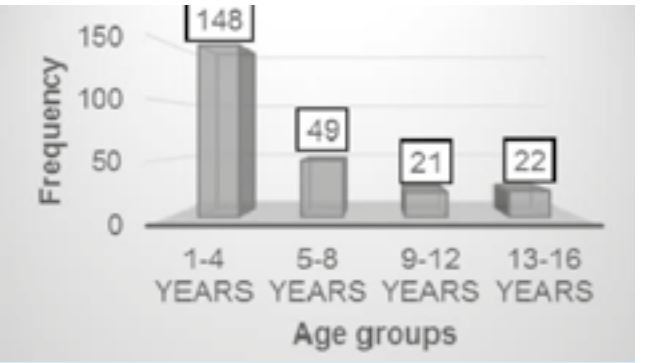

Fig-1. Age distribution of children

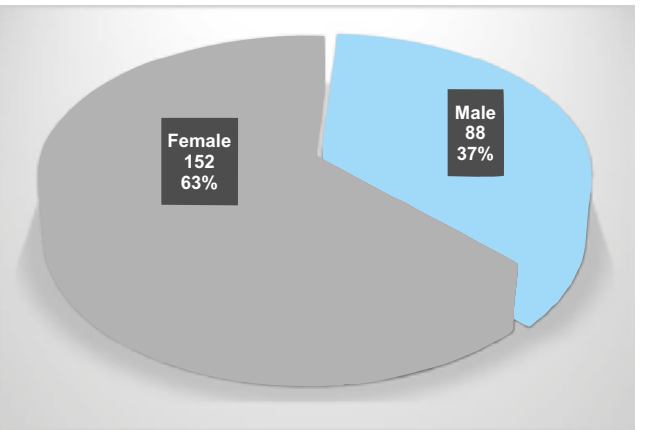

Fig-2. Distribution of gender of children

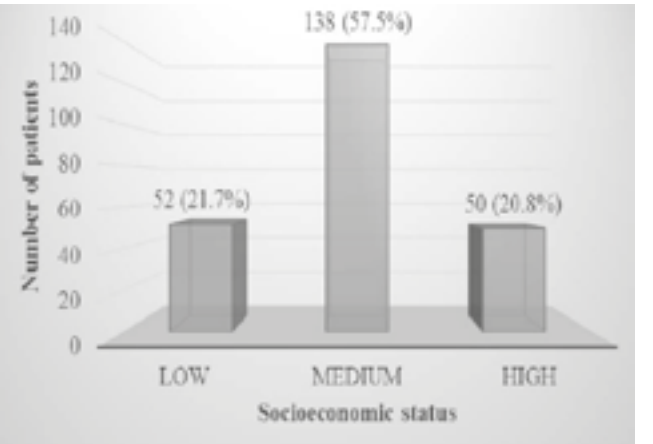

Fig-3. Distribution of children according to socioeconomic status of parents

To check that which variable (risk factor) is instigating the effect of other factors as insignificant in the model, stepwise logistic regression was run. The Cox & Snell R^2, of model 4 was highest i.e. 0.559 and Nagelkerke R^2 was also 0.745 for model 4 as compared to other models. When classification table was read, it was observed that

the overall percentage of model 4 was highest among overall percentage of model 1, 2 and 3 i.e., 89.6%, showing that model 4 is best to fit to see the effect of multiple factors for occurrence of PDA. Logistic regression is applied to see the effect of multiple risk factors on occurrence of PDA in children as a congenital problem, it was observed that family history, over the counter drugs or antibiotic use during pregnancy, Down's syndrome and preterm birth were significantly effecting the occurrence of PDA (P<0.05).

	OR	95% CI		p
		Upper limit	Lower limit	
Gender (Male / Female)	1.541	0.908	2.616	0.108
Positive Family history	1.676	0.856	3.282	0.130
Father smoker	1.541	0.908	2.616	0.108
Infection during pregnancy	49.333	21.873	111.267	0.000
Use of antibiotic or any other drug	53.200	22.926	123.449	0.000
Down's syndrome	10.818	1.362	85.896	0.005
Preterm birth	1.185	0.711	1.974	0.515

Table-II. Association of risk factor with PDA

	β	S.E.	Sig.	Exp(β)
Females gender	0.370	0.509	0.468	1.447
Family history	1.836	0.656	0.005	6.272
Father smoker	0.973	0.536	0.070	2.646
Infection during pregnancy	2.045	1.509	0.175	7.726
Over the counter drug use during pregnancy	4.778	1.815	0.008	118.845
Down's syndrome	5.484	1.536	0.000	240.852
Preterm birth	3.313	1.067	0.002	27.458
Constant	-31.752	6.117	0.000	0.000

Table-III. Logistic regression model showing effect of multiple risk on PDA

Logistic regression model 1:

$$PDA = \frac{\exp(1.447 \cdot \text{female gender} + 6.272 \cdot \text{family history} + 2.646 \cdot \text{father smoker} + 7.726 \cdot \text{infection during pregnancy} + 118.845 \cdot \text{antibiotic use} + 240.852 \cdot \text{Down's syndrome} + 27.458 \cdot \text{preterm birth})}{1 + \exp(1.447 \cdot \text{female gender} + 6.272 \cdot \text{family history} + 2.646 \cdot \text{father smoker} + 7.726 \cdot \text{infection during pregnancy} + 118.845 \cdot \text{antibiotic use} + 240.852 \cdot \text{Down's syndrome} + 27.458 \cdot \text{preterm birth})}$$

Logistic regression model 2:

$$PDA = \frac{\exp(5.031 \cdot \text{family history} + 674.713 \cdot \text{antibiotic use} + 343.032 \cdot \text{Down's syndrome} + 29.133 \cdot \text{preterm birth})}{1 + \exp(5.031 \cdot \text{family history} + 674.713 \cdot \text{antibiotic use} + 343.032 \cdot \text{Down's syndrome} + 29.133 \cdot \text{preterm birth})}$$

DISCUSSION

In our study, we included 240 children with the mean age of 4.86±4.01 years (range 1-15 years). There were >50% children presenting at age 1-4 years. The mean height and weight were 3.52±1.18 feet and 24.98±11.34 kg, respectively. There were 88(37%) males while 152(63%) were females. This showing that female gender is more common with the problem of PDA and as the number of females was more in case group so overall frequency of females was higher in this study. There were 174(72.5%) families of children who belonged (having residence) to urban area while 66(27.5%) families of children belonged to (living in) rural areas.

When odds ratio were calculated to see the effect of different risk factors on development of PDA, it was revealed that among cases, there were 50(41.7%) male children and 70(58.3%) female children. Among controls, there were 38(31.7%) male children and 82(68.3%) female children. The odds ratio was calculated as 1.541 (95% CI; 0.908, 2.616), showing that if gender of child is female at time of birth, there will be 1.5 times more chances of neonate to born with PDA. The difference was insignificant (P>0.05), but the female gender is found to be associated with PDA.

Among cases, there were 26(21.7%) children had positive family history while among controls, there were 17(14.2%) children had positive family history of PDA. In most of the cases, grandparents had history of PDA. The odds ratio was calculated as 1.676 (95% CI; 0.856, 3.282), showing that if family history of child is positive, there will be 1.7 times more chances of neonate to born with PDA. The difference was insignificant (P>0.05), but the positive family history of PDA is found to be associated with PDA.

Among cases, there were 82(68.3%) children whose fathers were smoker while among controls, there were 70(58.3%) children whose father were smoker. The odds ratio was calculated as 1.541 (95% CI; 0.908, 2.616), showing that if father is smoker and mother is a passive smoker, there will be 1.5 times more chances of neonate to born with

PDA. The difference was insignificant (P>0.05), but the smoking status of father is found to be associated with PDA. Among cases, mothers of 96(80%) children had history of severe infection during pregnancy of this particular child while among controls, mothers of 9(7.5%) children had history of severe infection during pregnancy of this particular child. The odds ratio was calculated as 49.333 (95% CI; 21.873, 111.267), showing that if mother would have severe infection including rubella during pregnancy, there will be 49 times more chances of neonate to born with PDA. The difference was significant (P<0.05), and infection during pregnancy is found to be associated with PDA.

Among cases, mothers of 95(79.2%) children reported that they used over the counter antibiotics or drugs for management of severe infection during pregnancy of this particular child while among controls, mothers of 8(6.7%) children reported that they used over the counter antibiotics or drugs for management of severe infection during pregnancy of this particular child. The odds ratio was calculated as 53.200 (95% CI; 22.926, 123.449), showing that if mother would use over the counter drugs or antibiotics to resolve their issue of infection or other problem during pregnancy, there will be 53 times more chances of neonate to born with PDA. The difference was significant (P<0.05), and use of medication without prescription of physician is found to be associated with PDA.

Among cases, 10 (8.3%) children had Down's syndrome while among controls, 1 (0.8%) children had Down's syndrome. The odds ratio was calculated as 10.818 (95% CI; 1.362, 85.896), showing that child had Down's syndrome; there will be 10.8 times more chances of neonate to born with PDA. The difference was significant (P<0.05), and Down's syndrome is found to be associated with PDA. Among cases, 70(58.3%) children had preterm birth while among controls, 65(54.2%) children had preterm birth. The odds ratio was calculated as 1.185 (95% CI; 0.711, 1.974), showing that child who had preterm birth, there will be 1.2 times more chances of neonate to born with PDA. The difference was insignificant (P>0.05), but preterm birth is found to be associated with PDA.

Karatza AA, Azzopardi D V and Gardiner HM concluded in their study that the occurrence of persistent PDA is common in preterm neonates and may be associated with more severe complications. Early precise diagnosis, evaluation of the significance of left to right shunt and rapid management are essential to improve the outcome in infants with PDA.[22]

Robida concluded that the frequency of PDA as an isolated disease in 5-10% of all congenital heart diseases. There is a left-to-right thrust from aorta to pulmonary artery triggering amplified pulmonary blood flow, left atrial and ventricular dilatation. The extent of shunt is highly dependent of size of PDA and ratio of systemic to pulmonary vascular conflict.[23]

In our study, logistic regression is applied to see the effect of multiple risk factors on occurrence of PDA in children as a congenital problem, it was observed that family history, over the counter drugs or antibiotic use during pregnancy, Down's syndrome and preterm birth were significantly effecting the occurrence of PDA (P<0.05), while female gender, smoking status of father and infection during pregnancy including rubella become insignificant (P>0.05).

Satoda, et al. found that PDA is comparatively common form of congenital heart ailment. While polygenic inheritance has been concerned, to date no specific gene defects have been identified which is instigating PDA. Therefore, a positional cloning approach was started to assess the gene responsible for PDA and associated physical conditions. Thus they conclude that a familial syndrome in which PDA is a common feature was mapped to a narrow region of chromosome 6p12-p21. Further analysis with other families and polymorphic markers and evaluation of potential candidate genes must clue to the identification of Char syndrome gene, which will provide insights into cardiogenesis as well as limb and craniofacial

development.[24]

Rather than preterm babies, in whom PDA for the most part is because of formative youthfulness, patent ductus in term newborns likely results from a critical basic variation from the norm. PDA happens with expanded recurrence in a few hereditary disorders, incorporating those with characterized chromosomal deviations, (e.g., trisomy 21 and 4p-disorder), single-quality changes, (for example, Carpenter's disorder and Holt-Oram disorder) and X-connected transformations (e.g., incontinentia pigmenti). Albeit most instances of PDA are apparently sporadic, many are accepted to be because of multifactorial legacy, with the prerequisite of hereditary inclination and an ecological trigger that happens at an exposed time.[25]

Hammoud, et al., in their study of frequency and risk factors associated with PDA in preterm neonates with respiratory distress syndrome in Kuwait. They tried to find that PDA is considered to be an important cause of morbidity and mortality among preterm infants. Hence the incidence of PDA in preterm infants with RDS in their study is similar to those reported from other countries. There are some risk factors that may detect neonates, who are more prone to PDA development, which required further prospective studies using a large sample size.[26]

Koch, et al. attempted to find that PDA conclusion happens inside 96 hours in >95% of neonates >1500 g in birth weight (BW). The pervasiveness and postnatal time of unconstrained ductal conclusion in neonates 1000g in BW (to a great degree low birth weight [ELBW] neonates) stay misty, as does the rate of inability to close with indomethacin. Consequently, they tentatively inspected the predominance, postnatal age, and clinical factors connected with unconstrained PDA conclusion, event of diligent PDA, and indomethacin disappointment in ELBW neonates. Along these lines they presume that unconstrained perpetual PDA conclusion happens in >34% of ELBW neonates and is anticipated by factors identified with development, while indomethacin disappointment couldn't be predicated.[27]

Korbmacher, et al. found that the hemodynamically relevant PDA weakens the pulmonary as well as cardiac function. In routine, PDA can be secured through surgery only. Thus they conclude that indomethacin is successful only in few cases. Early surgery is recommended.[28]

Fowlie et al., found that PDA and intraventricular drain (IVH) are both connected with expanded mortality and dreariness in preterm newborn children IVH in the neonatal period. There is however potential undesirable reactions of indomethacin, specifically a potential for lessened organ perfusion that may exceed any clinical advantages. The prophylactic utilization of indomethacin, where babies who might not have gone ahead to build up a symptomatic PDA or IVH would be presented to indomethacin, warrants specific examination. In this way they presume that Prophylactic treatment with indomethacin has various quick advantages, specifically a decrease in symptomatic PDA, the requirement for pipe ligation and serious IVH. Depending Indomethacin has been utilized effectively to treat symptomatic PDA and may likewise avoid or constrain on clinical conditions and individual inclinations, there might be a part for prophylactic indomethacin in a few babies on some neonatal units.[29]

CONCLUSION

We conclude that family history, over the counter drug use during pregnancy, Down's syndrome and preterm birth, are significant risk factors for development of PDA. It is noticed that some controllable factors like antibiotic intake during pregnancy without prescription of obstetrician and female should be aware of these factors which may lead their neonates to the hazardous disease.

Recommendations

These are the modifiable risk factors and can be controlled while female is pregnant except gender of baby. If these risk factors are controlled, then the frequency of PDA can be declined. This study

was conducted with a small sample size. If similar study would be done with large sample size, or at multicenter at district or provincial level, this could help in finding the extent of problem in local population and more awareness regarding risk factors. Following steps should be taken to have a healthy pregnancy and avoid PDA:

1. **Get early prenatal care, even before pregnancy:** Quitting alcohol and smoking (direct or indirect), avoid caffeine, avoid x-ray, reducing stress and medication during pregnancy particularly antibiotics.
2. **Eat a well-balanced diet:** Include a vitamin supplement that contains folic acid.
3. **Avoid infections:** should complete all of vaccinations before pregnancy. Certain types of infections can be harmful to a developing fetus. Also control glycemic level
4. **Family history:** If someone has family history of heart defects or other genetic disorders, consider talking with a genetic counselor before getting pregnant.

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