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Determinants Of Neonatal Jaundice Among Newborns In Pasir Puteh District, Kelantan.

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ABSTRACT

Background: Neonatal jaundice is one of the most common medical conditions in newborns. Knowing the predisposing factors of neonatal jaundice can be effective in controlling jaundice and the primary problem. Therefore, this study aimed to estimate the proportion of neonatal jaundice and its associated factors among newborns in Pasir Puteh district.

Materials and Methods: This study was a comparative cross-sectional study conducted in Pasir Puteh health facilities from August until September 2019 through retrospective record review of KIB205A birth registry, maternal and child health records. 140 randomly sampled newborns delivered between 1st January until 31st August 2019 were included in the study. Study proforma containing variables of interest were used for data collection to determine the associated factors for neonatal jaundice. Descriptive statistics and logistic regression were performed for data analysis.

Result: Out of 1154 newborns delivered between 1st January until 31st August 2019, 727 (63%) of them had neonatal jaundice. As for newborns with neonatal jaundice, their mean (±SD) for maternal age, gestational age and birth weight were 30.67 (±5.91) years old, 38.41 (±1.21) weeks and 3.02 (±0.46) kg, respectively. Newborns with neonatal jaundice mostly have non-diabetic mothers (74.3%), were delivered through vaginal delivery (84.3%) and male (61.4%). After adjusting the confounders by multiple logistic regression, diabetic mother [adjusted odds ratio (AOR) 4.66; 95% CI: 1.39, 15.63; p value =0.013], Caesarean delivery [AOR 5.34; 95% CI: 1.01, 28.38; p value=0.049] and male gender [AOR 2.61; 95% CI: 1.25, 5.45; p value=0.011] were the significant factors associated with neonatal jaundice.

Conclusion: This study provided important criteria to anticipate neonatal jaundice to improve the timely diagnosis and treatment in order to reduce the morbidity and mortality of neonates.

Keywords: neonatal jaundice, proportion, associated factors, Kelantan, Malaysia.

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1.0 Introduction

Neonatal jaundice (NNJ) or neonatal hyperbilirubinaemia is one of the most common medical conditions in newborn babies. All babies have a transient rise in serum bilirubin but only about 75% are visibly jaundiced (Ministry of Health, 2017). Jaundice is clinically detectable when the serum bilirubin levels are >85 μmol/L (5 mg/dl) (Ministry of Health, 2017). Neonatal jaundice is a common event that occurs especially in the first week of birth (Jardine & Woodgate, 2012; Paul, Lehman, Hollenbeak, & Maisels, 2006) and is one of the most common causes of hospitalization of the term and preterm neonates in neonatal wards (Jardine & Woodgate, 2012).

Jaundice on the first day of life is always pathologic, and urgent attention is needed to find its cause. Early jaundice is often due to hemolysis and internal haemorrhage (cephalohematoma, liver or spleen hematoma) or infection. Neonatal jaundice or physiological jaundice usually occurs on the second day of birth and is not usually harmful, and a self-limiting condition, where disease usually improves without treatment after reaching the normal amount of bilirubin (Ministry of Health, 2014), but very high levels of bilirubin may lead to kernicterus as permanent brain damage. Hyperbilirubinaemia is either unconjugated or conjugated. Without treatment, high levels of unconjugated bilirubin may lead to acute and chronic bilirubin encephalopathy. This may cause to neurodevelopmental problems including athetoid cerebral palsy, hearing loss and visual impairment (Ministry of Health, 2014). Diagnosis of neonatal jaundice and its management will play an important role in the health of newborns. If jaundice lasts more than 14 days, it is regarded as prolonged neonatal jaundice (Ministry of Health, 2017).

Identification of predisposing factors in the management of the disease is important (Mercier *et al.*, 2007). There are a number of predisposing factors in the occurrence of this disease, including Asian race, maternal diabetes, mothers with blood group O or Rhesus negative, prematurity, G6PD deficiency, polycythemia, male sex, cephalohematoma, medications, breastfeeding, delayed meconium passage and family history of jaundice (Boskabadi *et al.*, 2010; Engle, Tomashek, & Wallman, 2007; Linn et al., 1985; Maisels, Gifford, Antle, & Leib, 1988; Ministry of Health, 2017). The most common cause of jaundice can be ABO incompatibility (Haq, ul Haq, Khan, & Sayed, 2018; Idi *et al.*, 2019; Khurana, Batra, Faridi, & Khan, 2019). Type of delivery can be among the controversial factors in which Caesarean section predisposed to neonatal jaundice (Wijaya, 2017). Other known factors included congenital infections (syphilis, cytomegalovirus, rubella, toxoplasmosis), and maternal age more than 25 years (Zarinkoub & Beygi, 2007). To the best of our knowledge, there were no well-published study on the epidemiology of jaundice in Kelantan state.

Diagnosis and timely treatment of neonatal jaundice is critical to prevent its dangerous side effects. Knowing the predisposing factors of neonatal jaundice can be effective in controlling jaundice and the primary problem. Therefore, this study aimed to estimate the proportion of neonatal jaundice and its associated factors among newborns in Pasir Puteh district to improve the timely diagnosis and treatment in order to reduce the morbidity and mortality of hyperbilirubinemia.

International Journal of Public Health and Clinical Sciences
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2.0 Materials and Methods

From 1st August until 30th September 2019, a comparative cross-sectional study was conducted in six primary healthcare facilities in the district of Pasir Puteh, Kelantan. Pasir Puteh district is situated on the bank of Semerak River, about 30 kilometres to the south of Kota Bharu, the capital city of Kelantan state (Ishak, Awang, Aziz, Abdullah, & Bahari, 2019; MDPP, 2019). The clinics involved were Pasir Puteh Health Clinic, Selising Health Clinic, Cherang Ruku Health Clinic, Jeram Health Clinic, Gaal Health Clinic and Banggol Pak Esah Health Clinic.

The reference populations were all newborns with neonatal jaundice in Pasir Puteh district, and the study samples were all newborns with or without neonatal jaundice who fulfilled study inclusion and exclusion criteria in the six selected health clinics. The inclusion criteria were newborns delivered from 1st January 2019 until 31st August 2019 and underwent neonatal follow-up at any of the six recruited health clinics. Newborns with pathological jaundice were excluded from the study as pathological jaundice has discrepancy in term of the pathophysiology, hence its determinants are not comparable to physiological jaundice.

The sample size was calculated for each variable of associated factors neonatal jaundice among newborns using power and sample size calculation software (Dupont & Plummer Jr, 1990) as well to compare two independent proportions. The largest estimated sample for each group was 61 using the proportion of non-jaundice newborn by the factor of male (0.59) (Lake, Abera, Azeze, Gebeyew, & Demissie, 2019), an estimated proportion of 0.82, 5% type 1 error, 80% power and additional of 20% missing data. Therefore, the total sample size required was 140 newborns.

Data were collected from KIB205A birth registry (Ministry of Health, 2019) to determine the proportion of neonatal jaundice among total deliveries in Pasir Puteh district. Subsequently, 140 samples were randomly sampled and subdivided into jaundice and normal group to determine the associated factors for neonatal jaundice. Data on maternal and neonatal characteristics were extracted from home-based maternal and child health card, and subsequently recorded in patient's proforma. The retrieved information includes maternal characteristics (age, ethnicity, blood group, rhesus group, gestational or established diabetes, mode of delivery) and neonatal characteristics (gender, feeding type, gestational age, and birth weight).

We defined newborns with neonatal jaundice as newborn infants who developed jaundice during the first week of life with serum bilirubin levels >85 μmol/L (5 mg/dl) (Ministry of Health, 2017). Maternal diabetes is defined as mothers who had either established diabetes mellitus or gestational diabetes mellitus (IADPSG, 2010). Mixed feeding is defined as breastfeeding complemented with infant formula (Kurinij & Shiono, 1991). Normal birth weight is defined as weight of 2500 grams and above, while low birth weight is defined as weight less than 2500 grams (Hussain Imam, Ng Hoong, & Terrence, 2012).

International Journal of Public Health and Clinical Sciences
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November/December 2019

Data were analyzed by using SPSS software version 20. After checking the sample sets of the investigated values for the Kolmogorov-Smirnov distribution normality, it was revealed that the distribution of the investigated parameters were of normal distribution, that is why the methods of parametric statistics with mean and standard deviation calculation were used in the descriptive statistics besides frequency and percentages. Simple and multiple logistic regression analysis were used to determine factors associated with neonatal jaundice among newborns. All significant variables with a p-value <0.25 from univariable analysis and clinically important variables were chosen for multiple logistic regression analysis. A p-value<0.05 was considered statistically significant.

3.0 Result

From 1st January 2019 until 31st August 2019, based on KIB205A birth registry there were 1154 newborns delivered and underwent postnatal follow-up in the district of Pasir Puteh. Out of these 1154 newborns, 727 (63%) of them had neonatal jaundice as shown in Figure 1.

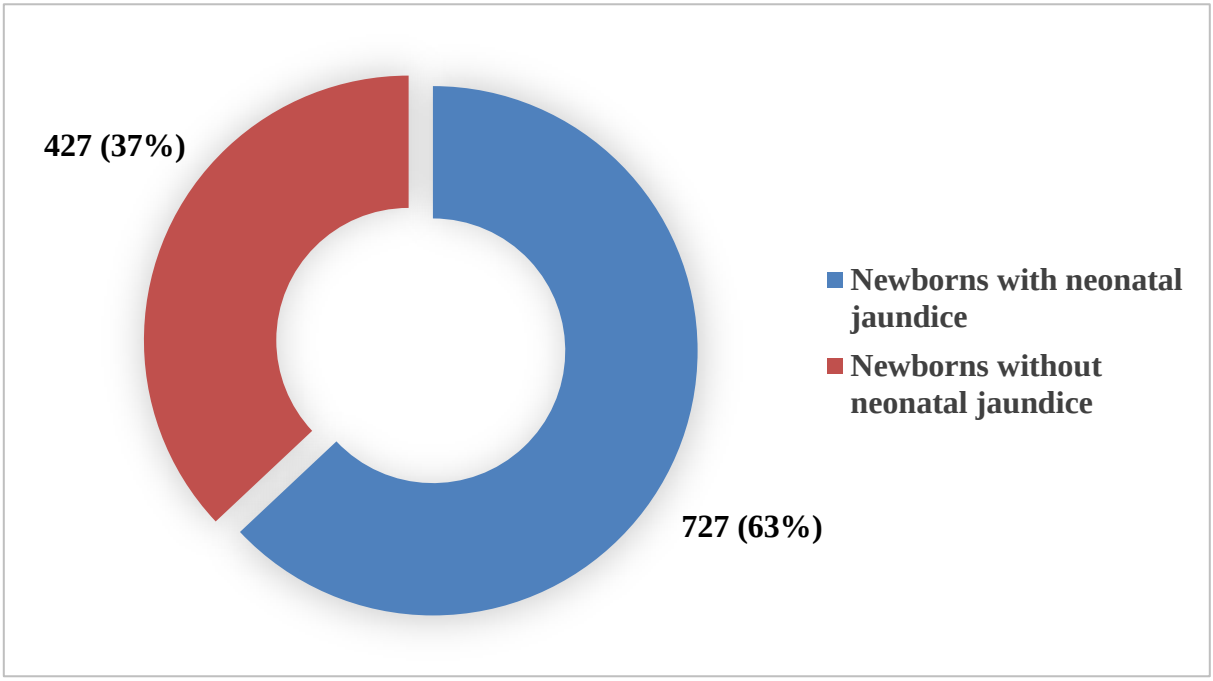

Figure 1: Proportion of newborns with neonatal jaundice among all newborns delivered in the district of Pasir Puteh, Kelantan (n=1154).

International Journal of Public Health and Clinical Sciences
e-ISSN : 2289-7577. Vol. 6:No. 6
November/December 2019

Out of 1154 samples found in the KIB205A birth registry, we did simple random sampling to recruit 140 samples, in which 70 newborns with neonatal jaundice and another 70 samples were normal newborns. For newborns with neonatal jaundice, their mean (±SD) for maternal age, gestational age and birth weight were 30.67 (±5.91) years old, 38.41 (±1.21) weeks and 3.02 (±0.46) kilograms, respectively. Majority of newborns with neonatal jaundice had maternal blood group O (41.1%), maternal Rhesus positive (90.0%), non-diabetic mothers (74.3%) and were delivered through vaginal delivery (84.3%). Majority of newborns with jaundice were male (61.4%), breastfed (94.3%) and had normal birth weight (90.0%). Details on maternal and neonatal characteristics are shown in Table 1 and Table 2.

Table 1: Maternal characteristics in accordance to jaundice outcome among newborns in Pasir Puteh district (n=140)

Characteristics	Frequency (%)	
	Jaundice newborns (n=70)	**Non-jaundice newborns (n=70)**
Maternal age (years)*	30.67 (±5.91)	29.74 (±5.63)
Maternal blood group		
AB group	5 (7.1)	7 (10.0)
A group	23 (32.9)	19 (27.1)
B group	13 (18.6)	24 (34.3)
O group	29 (41.4)	20 (28.6)
Maternal Rhesus group		
Positive	63 (90.0)	68 (97.1)
Negative	7 (10.0)	2 (2.9)
Mode of delivery		
Vaginal delivery	59 (84.3)	68 (97.1)
Caesarean section	11 (15.7)	2 (2.9)
Maternal diabetes		
No	52 (74.3)	66 (94.3)
Yes	18 (25.7)	4 (5.7)

*Mean (±SD)

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Table 2: Neonatal characteristics in accordance to jaundice outcome among newborns in Pasir Puteh district (n=140)

Characteristics	Frequency (%)	
	Jaundice newborns (n=70)	**Non-jaundice newborns (n=70)**
Gestational age (weeks)*	38.41 (±1.21)	38.33 (±1.32)
Birth weight (kilograms)*	3.02 (±0.46)	3.02 (±0.34)
Gender		
Female	27 (38.6)	45 (64.3)
Male	43 (61.4)	25 (35.7)
Feeding type		
Mixed	4 (5.7)	3 (4.3)
Breastfeeding	66 (94.3)	67 (95.7)
Birth weight category		
Normal weight	63 (90.0)	64 (91.4)
Low birth weight	7 (10.0)	6 (8.6)

*Mean (±SD)

Variables with p<0.25 in the univariable analysis (simple logistic regression) were maternal diabetes status, maternal Rhesus group, modes of delivery and gender of neonates. Multiple logistic regression analysis revealed diabetic mothers, Caesarean section and male gender were the significant associated factors for neonatal jaundice among newborns in Pasir Puteh district (Table 3).

Table 3: Factors associated with neonatal jaundice among newborns in Pasir Puteh district (n=140).

Factors	β	S.E.	Wald statistics (df)	Adjusted OR (95% CI)	*p*-value
Mode of delivery					
Vaginal delivery				1.00	
Caesarean section	1.68	0.85	3.87 (1)	5.34 (1.01, 28.38)	0.049*
Maternal diabetes					
No				1.00	
Yes	1.54	0.62	6.23 (1)	4.67 (1.39, 15.63)	0.013*
Gender of neonate					
Female				1.00	
Male	0.96	0.38	6.50 (1)	2.61 (1.25, 5.45)	0.011*

*p-value <0.05. Forward LR method applied.
No multicollinearity and no interaction found.
Hosmer Lemeshow test, p-value=0.781
Classification table 68% correctly classified.
Area under Receiver Operating Characteristics (ROC) curve was 72.6%.

4.0 Discussion

The proportion of neonatal jaundice in Pasir Puteh district in the first eight months of 2019 was 63%. Our finding is substantially higher than the finding from another local study conducted in 2013 in Seremban district, Negeri Sembilan which was only 16.4%. Their study defined hyperbilirubinemia as a total serum bilirubin level of ≥250 µmol/l (Wong, Boo, & Othman, 2013). Our study attained higher proportion of neonatal jaundice as we followed the lower diagnostic level for hyperbilirubinemia set forth by the Ministry of Health which is 85 µmol/l

(5mg/dL) (Ministry of Health, 2017), resulting in more babies being diagnosed with neonatal jaundice.

For cross-country comparison purpose, the mean (±SD) of maternal age in our study is slightly higher (30.67±5.91) than then mean maternal age in a study done in Kerala, India (25.97±4.54 years) (Menon & Amanullah, 2017). A study by Mojtahedi *et al.* (2018) in Iran reported almost similar finding in term of blood group; but showed substantial discrepancy in term of Rhesus group. Neonatal jaundice was found in 40.5% of mothers with O-blood group in Iranian study and 41.5% in our study; and 77.0% of mothers with Rhesus positive in Iranian study as compared to 90% in our study (Mojtahedi *et al.*, 2018). As for method of delivery, our study reported higher proportion of neonatal jaundice in babies delivered vaginally (84.3%) as compared to a study conducted in Iran which was only 41.0% (Tavakolizadeh *et al.*, 2018). As for maternal diabetes, our study exhibited similar finding with the Iranian study which is majority of infants with neonatal jaundice belonged to non-diabetic mothers (74.3% versus 76.5%, respectively) (Tavakolizadeh *et al.*, 2018).

For neonatal factors, we found that 90.0% of our newborns who has jaundice has normal birth weight. However in an Indian study, low birth weight babies (<2.5kg) were more likely to get neonatal jaundice (Menon & Amanullah, 2017). Lake et al. (2019) found that majority (64.8%) of newborns in Ethiopia were born at term (≥37 weeks gestation) which was congruent to our study finding. As for gender, Oppong *et al.* (2019) reported 35.2% of infants with neonatal jaundice in Ghana were male which is lower than our finding (61.4%). As for type of feeding practices, 94.3% of our breastfed infants had neonatal jaundice as compared to only 22.3% in Ghana (Oppong *et al.*, 2019).

The result of our study showed that neonates delivered through Caesarean section were more likely to get neonatal jaundice as compared to neonates of vaginal delivery. This finding is congruent to many other studies worldwide reporting significant association between Caesarean section with neonatal jaundice (Chew & Swann, 1977; De Amici *et al.*, 2001; Geller, Wu, Jannelli, Nguyen, & Visco, 2010; Wijaya, 2017). It is postulated that anaesthesiologic strategies for Caesarean section particularly the use of isoflurane and bupivacaine groups during Caesarean section procedure induced substantial rise in the total bilirubin levels of neonates (De Amici *et al.*, 2001; Wijaya, 2017).

In our current study, infants of diabetic mothers were more likely to get neonatal jaundice which is similar with studies in Israel and Germany (Gale, Seidman, Dollberg, & Stevenson, 1990; Jährig *et al.*, 1989). A study by Jährig *et al.* (1989) in Karlsburg, Germany showed that infants of diabetic mothers developed higher bilirubin levels after the third day of life as compared with infants of non-diabetic mothers. This finding could be explained in a complex physiological mechanism. Infants of diabetic mothers tend to have hyperinsulinemia due to hyperplasia of fetal pancreatic beta cells consequent to maternal-fetal hyperglycemia. Starvation will later cause induction of microsomal heme oxygenase which consequently increased bilirubin formation (Jährig *et al.*, 1989; Mitanchez *et al.*, 2015). To some extent the polycytaemia typical in infants

of diabetic mothers acts as an additional factor, capable of stimulating the bilirubin turnover, as does the decrease of bilirubin excretion by the liver (Jährig *et al.*, 1989).

We also found a significant association between male gender with neonatal jaundice, when other confounders were adjusted. This finding is in line with studies in the United States of America, China and Nepal where male neonates were more likely to get neonatal jaundice as compared to female neonates (Fok *et al.*, 1986; Scrafford *et al.*, 2013; Tioseco, Aly, Milner, Patel, & El-Mohandes, 2005). The basis for this sex-related difference in the incidence of neonatal jaundice in unclear, but study on rats pointed out to potential role of sex hormones as regulator of bilirubin conjugation. Hepatic conjugation of bilirubin and bilirubin clearance rate are higher in females than in males (Rosenthal, Pincus, & Fink, 1984; Watchko & Lin, 2010). Besides that, systemic development and maturation process in males were slower than females. It might therefore be possible that male neonates have also a less mature hepatic bilirubin conjugating enzyme system as compared to female neonates (Fok *et al.*, 1986).

There were some limitations in this study. We did not include ABO incompatibility as one of the studied factors because it will incur more cost to our health facilities to do blood grouping to non-jaundice newborns. Besides, it is unethical and not medically indicated to administer unnecessary testing to them. Data on G6PD status of newborns is not well-documented in most of the home-based child health card, and hence we need to exclude that variable as well from our study. Since ABO incompatibility and G6PD-deficiency are already well-studied worldwide and are well-known as significant associated factors for neonatal jaundice (Akgül, Korkmaz, Yiğit, & Yurdakök, 2013; Idi *et al.*, 2019; M Abo El Fotoh & Rizk, 2016; Olusanya, Mabogunje, Aina, & Emokpae, 2018; Owa, Durosinmi, & Alabi, 1991), it's more beneficial and economical to explore other contributing factors which are still under-explored.

5.0 Conclusion and recommendation

In summary, neonatal jaundice is quite prevalent in the district of Pasir Puteh as the proportion was 63%. Caesarean section, maternal diabetes and male gender of neonate were the significant associated factors for neonatal jaundice in the district of Pasir Puteh, Kelantan. As those factors can usually be detected or screened prior to delivery of infants, we may anticipate development of neonatal jaundice in infants presented with the highlighted risk factors, and indirectly facilitate healthcare personnel to diagnose neonatal jaundice. High index of suspicion for neonatal jaundice in infants with the risk factors discussed above will improve the timely diagnosis and treatment in order to reduce the morbidity and mortality of neonates.

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Declaration

The authors declare that this manuscript has never been published in any other journal.

Authors contribution

Author 1: Conceptualization, information gathering, data entry, data analysis, manuscript drafting, editing and review.
Author 2: Conceptualization, information gathering, manuscript drafting and review.
Author 3: Conceptualization and information gathering, manuscript review.
Author 4: Conceptualization, technical and logistic support, and manuscript review.

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