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## Aetiology of neonatal jaundice in apparently well late-preterm and term neonates at a mission hospital, Southwestern Nigeria

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### Abstract: Background

The knowledge of the aetiology for neonatal jaundice is important in the early detection and effective management of infants with or at risk of severe jaundice before hospital discharge. This study assessed the aetiological factors of neonatal jaundice among apparently well late preterm and term-newborns to ensure timely intervention where these risk factors exist.

**Method:** This was a cross-sectional study involving 174 apparently well neonates at a tertiary mission hospital. Detailed history, physical examination, relevant haematological and biochemical tests were undertaken. Significant jaundice was defined as serum bilirubin greater than 2 standard deviations above the postnatal age and weight dependent treatment concentration.

**Results:** Of the 844 neonates admitted into the neonatal care unit, 174 (20.6%) had significant jaundice. Median age at presentation was 3days (95% CI of median 3-4days). The mean  $\pm$ SD gestation

age and birth weight of the neonates at recruitment were  $38.1 \pm 1.6$  weeks and  $3.1 \pm 0.5$ kg respectively. Males were 108 (62.4%; M: F.1.6.1). The mean  $\pm$ SD total serum bilirubin was  $13.9 \pm 4.7$ mg/dl. Significant jaundice was more common with maternal-baby concordant paired blood group of A-A, O-O compared with discordant materno-baby group pairs. Of the known causes of significant neonatal jaundice, G6PD deficiency (57-38.5%) ranked topmost. Half (87-50.0%) of the causes of significant jaundice were unidentified.

**Conclusion :** G6PD deficiency remains the leading aetiology for significant neonatal jaundice. G6PD screening should be mandated before hospital discharge, compatible mother-baby blood group pairs do not rule the risk for significant jaundice; further research is required to elucidate other inherent unidentified aetiologies.

**Key words:** neonatal hyperbilirubinaemia, G6DP, significant jaundice, late pre-term

### Introduction

Neonatal hyperbilirubinaemia is a common condition in neonates affecting up to 8 in 10 newborns in the first week of life.<sup>[1,2]</sup> It is often a benign condition but up to 35% of neonatal hospital admissions may be consequent on significant hyperbilirubinaemia requiring treatment in the first week of life.<sup>[3]</sup> Early post-natal discharge without early follow up has increased the burden of severe jaundice and delayed presentation in recent times.<sup>[4,5]</sup> Given the adverse consequences attributable to severe jaundice such as acute bilirubin encephalopathy (ABE) and subsequent kernicterus spectrum disorders, various intervention and risk assessment tools have been put in place for the identification of babies at risk of severe NNJ.<sup>[2,6]</sup> The universal neonatal jaundice risk assessment and screening rightly advocate early neonatal

screening and assessment for jaundice in the first 48 hours of life, and prior to discharge from the hospital with a recheck at short term follow-ups.<sup>5,7-10</sup> Khairy *et al*<sup>11</sup> have reported that cord blood bilirubin/albumin ratio is a good predictor of significant neonatal jaundice. Many authors have suggested that percentage weight loss and peaked serum bilirubin levels during the first 3 days of life are sensitive predictors of hyperbilirubinaemia among term and late preterm neonates on exclusive breastfeeding.<sup>1,3,11-13</sup>

Similarly, Han *et al*<sup>14</sup> reported that gestational age, male gender, family history of previous neonatal jaundice requiring phototherapy, bruising, feeding mode, weight loss, and early discharge are predictors of post-discharge significant hyperbilirubinemia among a Chinese cohort. In several studies and consistently over the years, G6PD

deficiency is not only a leading cause of significant jaundice but is also associated with jaundice related morbidity and death.<sup>2,15-18</sup> Slusher *et al*<sup>15</sup> reported a 36% prevalence of G6PD deficiency in babies with significant jaundice while a slightly higher percentage (47.7%) were identified by Oseni *et al*<sup>16</sup> in Southwestern Nigeria. These reports were similar to observations from the other part of the country.<sup>18-20</sup> Mothers with blood group O setup and Rhesus iso-immunization are established risk for significant jaundice. However, iso-immunization appears to run as the least reported risk in several studies in Nigeria.<sup>21-23</sup>

The published predictors of significant jaundice can be extrapolated for other populations, though; some of these specific aetiologies are known to vary from one country to another and among different regions within the same country. The relatively small sample size of published literature and the limited systematic review on aetiology of neonatal jaundice give credence to initial local studies to establish the profile of aetiology in each locality.

The current knowledge of ABO haemolytic disease of newborns largely covers the interaction between red blood cells ABO antigens and circulating ABO antibodies. Little attention has been given to the risk for significant jaundice in ABO group compatible blood in general. In addition, the role of other known and latent red blood cell surface markers such as the P, Duffy and Dombrock blood group systems which are often not measured, especially in group compatible blood are untapped.<sup>24</sup> What impacts do other cellular and humoral factors in group compatible mother-baby pairs play in the development of significant neonatal jaundice? These are some of the unanswered questions calling for continual research for clarity. Maisels in a review had documented that haemoglobinopathies such as alfa and beta thalassemsias, unstable haemoglobin and other forms of enzymopathies are known causes of significant jaundice.<sup>25</sup>

The study aimed to determine the prevalence and aetiologies of neonatal hyperbilirubinaemia in apparently well babies. It is hoped that this study, apart from providing information, will stimulate further research in this field.

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## Methods

The Bowen University Teaching Hospital is an offshoot of the Baptist global mission of the Nigerian Baptist Convention. The neonatology unit of the department of Paediatric has its workforce consisting of Nigerian nationals and volunteered expatriates Christian doctors who provide clinical services to newborns at the unit. The expatriates completely support the treatment of babies with significant jaundice, they provide the transcutaneous bilirubinometer, an irradiance meter and either filtered sunlight phototherapy or electrically phototherapy for the treatment of significant jaundice.

This was an observational cross-sectional study conducted between July 31 2015 and April 30 2017 among apparently well neonates presenting with jaundice at the Bowen University Teaching Hospital Ogbomosho, Nigeria.

The hospital Human Research Ethics Committee granted ethical approval for the study and informed consent was obtained from the parents/caregivers. Included in the study were apparently well late preterm and term neonates aged 14 days or younger. Also neonates with total serum bilirubin concentrations at or higher than the post-natal age-dependent treatment concentrations as recommended by the American Academy of Pediatrics for high risk patients.<sup>26</sup> Exclusions included neonates who required treatment of conditions other than jaundice, had gross congenital anomalies, had blood transfusion before referral to the centre, and those with clinical or laboratory features of septicaemia, or who were unlikely to survive the first 24 h of life as judged by clinicians.

Sample size for the study was determined using Fischer's formula at a 35% incidence rate previously reported in Nigeria.<sup>31</sup> Consecutive newborn neonates who presented to the facility with jaundice and who met the eligibility criteria were recruited into the study.

Detailed history including socio-demographics, perinatal, maternal history and information on parents' blood group were obtained. Eligible neonates had physical examination for levels of clinical pallor and jaundice. A transcutaneous bilirubinometer (JM-103 Draeger Medical) was used to screen newborns for jaundice in the lying-in-ward. Significant jaundice was defined as serum bilirubin greater than 2 standard deviations above the norm for age and weight based on the recommendation on Clinical Practice Guidelines by the American Academy of Paediatrics(AAP).<sup>26</sup> Three millilitres of blood was aseptically drawn from a carefully selected vein at the dorsum of the hand into an ethylenediaminetetraacetic (EDTA) bottle for haematological test. Total serum bilirubin concentration was measured with an Advanced BR2 Stat-Analyzer (Advanced Instruments, Norwood, MA, USA). The blood group of mothers and neonates were determined by tiles and slide methods.<sup>27</sup> The blood was centrifuged at 1000c/pm and the packed cell volume was measured using the micro-haematocrit. A child is said to have ABO haemolytic disease and G6PD deficiency when the Direct Coomb's test was positive and there were evidences of haemolysis on the peripheral blood smear.

Neonates with significant jaundice were exposed to either filtered sunlight phototherapy or conventional electrical phototherapy of locally fabricated aluminium frame fitted with three or five blue light-emitting diode tubes, with each tube having nine light-emitting diodes that delivers up to 30  $\mu\text{W}/\text{cm}^2/\text{nm}$  of irradiance. The intensity of phototherapy was monitored using BiliBlanket II spectrometer (GE Healthcare, Chicago, IL, USA). Data collected was analysed using the IBM Statistical Package for Social Sciences (SPSS)<sup>™</sup> version 23.0 for windows. Frequency distribution tables of variables

were generated. Measures of central tendency (mean, median and mode) and dispersion (standard deviation, variance) of quantitative variables were determined. Neonates' age was not normally distributed and was represented in median. Differences between proportions of categorical variables were evaluated using the Chi-square test or the Fischer's exact test. The confidence level was set at 95% and the level of significance at  $p < 0.05$ .

**Results**

Of the 844 neonatal admissions over the study period, 174 had significant neonatal jaundice equalling 206 cases/1,000 neonates. Median age at presentation was 3-days; 95% CI (3.0-4.0 days). Most of the neonates were inborn 122(70.5%). The mean  $\pm$  SD gestation age and birth weight of the neonates were  $38.1 \pm 1.6$  weeks and  $3.1 \pm 0.5$  Kg, respectively. There were 108 (62.4%) males and 65 (37.6 %) females giving a M: F of 1.7:1 ( $X^2=21.68, p < 0.001$ ). Other details are as shown in Table 1.

**Table 1:** Sociodemographic and clinical characteristics of the neonates

Variable	Number (n)	Percentage (%)
Age (days)	Median(95% CI of median) 3(3-4days)	
0-7	167	96
Aug-14	7	4
<i>Gender</i>		
Female	65	37.6
Male	108	62.4
<i>Place of Birth</i>		
BUTH	122	70.5
Other Hospital	27	15.6
Home	4	2.3
Clinic	5	2.9
Church	9	5.2
Other	6	3.5
<i>Gestational Age (weeks)</i>		
34-36	36	20.8
37-39	93	53.2
40-42	45	26
<i>Birth Weight (kg)</i>		
<2.5	19	10.4
2.5-3.9	152	87.9
>3.9	3	1.7

BUTH \*Bowen University Teaching Hospital, Ogbomosho

*The causes of significant neonatal jaundice*

About half 87 (50.0%) of the neonates with significant jaundice had no identifiable cause. Glucose 6 phosphate dehydrogenase deficiency accounted for 57 (32.7%) of the known causes of neonatal jaundice. ABO incompati-

bility and Rhesus isoimmunisation were responsible for 22(12.6%) and 8(4.6%) cases of significant jaundice.

Table 2. Shows the laboratory results of neonates with significant jaundice.

The mean  $\pm$  SD haematocrit of the neonates was  $45.4 \pm 7.3\%$ . With respect to the blood group of the newborns, 86 (49.7%) had blood group O while 43 (24.9%) had blood group B. Similarly, groups O (108-62.0%) and B (33-(18.7%) were the most frequent blood groups in the mothers. Only 9 (4.9%) mothers were Rhesus negative. Haemolysis in ABO haemolytic disease and G6PD deficiency were confirmed with the Direct Coomb's test positive and evidences of haemolysis on the peripheral blood smear. Other details are shown on table 2.

**Table 2:** Laboratory result of neonates and their mothers

Variables	Frequency	Percentage
<i>Mother's blood group</i>		
A	33	18.7
B	28	16.3
AB	5	3.0
O	108	62.0
Rhesus positive	165	95.1
Rhesus Negative	9	4.9
<i>Baby's blood group</i>		
A	39	22.0
B	43	24.9
AB	6	3.5
O	86	49.7
Rhesus positive	169	96.9
Rhesus Negative	5	3.1
Direct combs test	22	12.6
Serum bilirubin	13.9 $\pm$ 4.7mg/dl	
Packed cell volume	45.4 $\pm$ 7.28	

Tables 3 Shows association between significant jaundice and paired concordant Mother-Baby's blood group.

Of the 108 mothers with blood group O, 72/108 (67.37%) neonates with concordant mother-baby blood group O-O had significant jaundice compared with non-concordant pairs with blood group O mothers (36/108-33.3%;  $p < 0.0001$ ). Similarly, 21/33 (63.6%) neonates with concordant mother-baby pairs blood group A-A had significant jaundice compared with non-concordant pairs with blood group A mothers (12/33 -36.3%;  $p=0.028$ ). There were 28 blood group B mothers and 17 concordant mother-baby pairs blood group B-B , 17/28 ( 60.7%) when compared with non-concordant pairs with blood group B mothers 11/28-39.3% ( $p= 0.112$ ) Other details are shown in Table 3

**Table 3:** Paired mother- baby;s blood Group and significant jaundice

		Baby's Blood Group				Total
		A	B	AB	O	
Mothers Blood Group	A	21(63.6)	2(6.1)	2(6.1)	8 (24.2)	33(100.0)
	B	2(7.1)	17(60.7)	3(10.7)	6 (21.4)	28(100.0)
	AB	0(0.0)	5(100.0)	0(0.0)	0(0.0)	5(100.0)
	O	15(14.0)	19(17.8)	1(0.9)	72 (67.3)	107(100.0)
Total		38(22.0)	43(24.9)	6(3.5)	86 (49.7)	173(100.0)

**Discussion**

Neonatal jaundice remains a major challenge and a cause of neonatal morbidity and mortality in sub-Saharan Africa. The result of this study shows that G6PD deficiency is the leading identifiable cause of neonatal jaundice in our centre. This is similar to what has been reported in literature especially in the West African sub region.<sup>23</sup> Our results, however, differ from the findings by Adoba et al<sup>12</sup> in Ghana, reported that only 12% of significant jaundice in their study was attributable to G6PD deficiency.<sup>12</sup> The reason for the higher prevalence in our study might be because we studied only apparently well neonates while the study in Ghana included sick neonates, who may have had other causes of jaundice that may affect the proportional prevalence due to G6PD deficiency.

The present study also found male preponderance in the pool of newborns with significant jaundice, this is in tandem with the report by Awang et al.<sup>13</sup> The reason for the male preponderance may be linked to the higher prevalence of G6PD deficiency in the West African sub population. G6PD deficiency is an X-linked autosomal recessive disorder with a propensity for the male gender.

The ABO set up of mother with blood group O and neonates with other blood group was a less common cause of significant jaundice in this study and this is in line with previous observations.<sup>21, 23</sup> Kalakheti<sup>28</sup> in Kathmandu however reported ABO incompatibility as a major cause of neonatal hyperbilirubinaemia in the study population. The present study was a cross sectional design in which newborns with significant jaundice were recruited as against the Kathmandu<sup>28</sup> study where only mothers with the ABO set up for neonatal jaundice were enrolled. Thus the result may be biased by the study design.

Of interest is the finding of higher prevalence of jaundice in concordant mother-baby pair and G6PD sufficient neonates when compared with mother-baby blood group discordant pairs. According to the findings of this study, mother-baby pairs with compatible blood groups (e.g. mother-baby pairs with blood groups A-A, O-O

pairs have a statistically significant higher risk of developing neonatal hyperbilirubinaemia. The reason behind the high prevalence of significant jaundice in concordant pairs remains unclear and warrants more research. What we know is that the reason is not related to ABO haemolytic disease. The ABO haemolytic diseases are a rare cause of significant jaundice among neonates of African descent.<sup>[23]</sup> Some plausible explanations for this phenomenon are many. Besides, the ABO blood group system are the minor blood group systems whose roles in neonatal jaundice are still understudied. These minor group systems such as of P, P1 and Pk of the P blood group system, fya-b+ and fya-b- of the Duffy blood group system and the Dob antigen of the Dombrock blood group system to mention a few. Perhaps the minor blood group system may be co-factor for the ABO phenotype but not a standalone risk for significant jaundice.

Other reasons for an increased prevalence of jaundice in concordant mother-baby blood groups could be explained based on the documented blood group O differing receptor avidity levels for specific pathogens (e.g. bacteria, viruses and parasites) as well as toxins that can enhance invasion, colonisation and internalisation of these pathogens or toxins, which are considered triggers or inducers of haemolysis. A typical example is an association observed between blood group O phenotype and an increased risk of Escherichia coli infection, a leading cause of neonatal sepsis. Perhaps the ‘two-hit’ theory effect of a mother having the same blood phenotype as her baby may imply double jeopardy with enhanced susceptibility to sepsis-induced haemolysis. But this cohort does not include neonates with sepsis and therefore may not suffice as an independent risk in this scenario.

The finding of half of the present population having no identified risk from the basic laboratory test for previously documented risk is also a stimulus for thought. There is a need not to only focused on examining the traditional risk factors for significant jaundice if the sustainable development goal 3 will be extended to the newborns in the 21<sup>st</sup> century.

Further research is required is investigate the molecular basis and other immunological factors that may enhance haemolysis in sub-populations of newborns with compatible blood groups. There is also a need to elucidate the inherent susceptibility factors in mother-neonate pairs for risk assessment and proper planning especially where healthcare delivery still largely hovers around primary prevention, diagnosis are usually delayed with limited resource for intensive care.

**Conclusion/recommendations**

G6PD deficiency remains the leading aetiology for significant neonatal jaundice. Compatible mother-baby blood group pairs do not rule the risk for significant

jaundice; further research is required to elucidate other inherent unidentified aetiologies. This study recommends that G6PD screening should be mandated before hospital discharge. It is time to explore other causes of significant jaundice in apparently well babies in our population besides the traditional aetiologies of G6PD and ABO iso-immunization.

### Author Contributions

MAA: Contributed to acquisition, analysis, or interpretation of data; drafted the manuscript; critically revised the manuscript for important intellectual content; gave final approval; agree to be accountable for all aspects of the work in ensuring that questions relating to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

OYT: Critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

TOO Substantially contributed to the design, acquisi-

tion, analysis, or interpretation of data; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

STM: Contributed conceptualization of the work, the design; acquisition; drafting, critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

AOT: Contributed to acquisition, analysis, or interpretation of data; drafted the manuscript; critically revised the manuscript for important intellectual content; gave final approval; agree to be accountable for all aspects of the work in ensuring that questions relating to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

DAG: Contributed conceptualization of the work, the design; acquisition; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

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