ORIGINAL ARTICLE

Treatment Outcome of Hyperbilirubinaemia Among Icteric Neonates in Jos: The Impact of Glucose-6-Phosphate Dehydrogenase Status

Ezra D **JATAU**[1]
Bose O **TOMA**[2]
Julie O **EGESIE**[1]
Obadiah D **DAMULAK**[1]
Victoria T **MA'AN**[1]

[1]*Department of Haematology and Blood Transfusion*
[2]*Department of Paediatrics*

Jos University Teaching Hospital
Jos, NIGERIA

Author for Correspondence
Dr Jatau Ezra **DANJUMA**
Department of Haematology and Blood Transfusion
Jos University Teaching Hospital
Jos, NIGERIA

Phone: +234 806 540 3375
Email: ezradjatau@gmail.com
Jatauez@unijos.edu.ng

Received: May 12th, 2020
Accepted: July 14th, 2020

DISCLOSURE
No conflict of interest declared by the authors

ABSTRACT

Background: Hyperbilirubinaemia is a common clinical manifestation of several neonatal disorders, one of which is Glucose-6-Phospate Dehydrogenase(G6PD) deficiency.

Objective: To determine the treatment outcome of hyperbilirubinaemia in relation to the G6PD status of icteric neonates in our environment.

Methodology: This was a cross sectional study of 150 icteric neonates enrolled consecutively as they were admitted into the Special Care Baby Units (SCBUs) of the Jos University Teaching Hospital, Bingham University Teaching Hospital, and the Plateau State Specialist Hospital. The neonates were reviewed clinically for fever, jaundice, cyanosis among other features. Blood sample was collected for Full Blood Count (FBC), Reticulocyte Count, Serum Bilirubin (SB) and G6PD assay using the Pointe Quantitative Diagnostic Kit (USA). G6PD deficiency was defined by enzyme activity < 6.0 IU/gHb.

Results: Subjects comprise of 92 (61.3%) males and 58 (38.7%) females (M: F= 1.6:1) with median age at presentation of 3 (Interquartile range-IQR: 1-4) days. One hundred and five (70%) were delivered at full-term gestation (≥37weeks) while 45 (30%) were delivered preterm(37weeks). Twenty-nine (19.3%) had history of jaundice in siblings. Fifty (35.7%) had birth weight < 2500g while 90 (64.3%) have normal birth weight. Their mean haemoglobin concentration was 15.90 ± 2.23 g/dl while median reticulocyte count was 2.5 (IQR: 2-3) %. Sixty-one (40.7 %) of the studied neonates were G6PD deficient with mean G6PD activity of 3.99(IQR: 2.72-4.94) IU/gHb and median concentration of total serum bilirubin of 205(IQR: 170.0-281.6) µmol/L. Mode of treatment of hyperbilirubinaemia in 88 (58.7%) of the studied subjects was by phototherapy, with 36 (59.0%) of them G6PD deficient. Sixty-two (41.3%) were treated with phototherapy and exchange blood transfusion. One hundred and twenty-two (81.3%) of all the subjects were discharged home fully recovered, 2 (1.3%) had acute bilirubin encephalopathy while mortality was recorded in 14 (9.3%).

Conclusion: Significant populations of icteric neonates in our environment are G6PD deficient and they turn out with a relatively good treatment outcome irrespective of their G6PD status.

Key words: *Exchange blood transfusion, DAMA, Jaundice, Phototherapy*

INTRODUCTION

Glucose-6-phosphate dehydrogenase (G6PD) is a key enzyme in the pentose phosphate pathway required for the formation of glutathione, a crucial antioxidant with ability to effectively counter the damaging and toxic effect of oxygen on haemoglobin and red blood cells (RBC).[1] Individuals with G6PD deficiency suffer reduced antioxidant activity with the consequence of haemolysis, anaemia, hyperbilirubinaemia and attendant complications.[1]

The gene encoding for G6PD is located on the long arm of the X-chromosome and hence the enzyme deficiency is inherited as an X-linked disorder.[1] G6PD deficiency affects about 1% of the World's population, with highest prevalence among males of West African, Mediterranean and South-East Asian descent.[2] Prevalence of G6PD deficiency in Nigeria ranges from 4-26% in the general population while jaundiced neonates have a G6PD prevalence of up to 43%; sometimes presenting with features of severe hyperbilirubinaemia that could cause kernicterus or death.[3,4]

Management of hyperbilirubinaemia in G6PD deficient individuals is centered on avoiding oxidant stress like drugs, chemicals, fava beans known to trigger haemolysis resulting in the hyperbilirubinaemia.[5] Phototherapy is the initial specific treatment modality for neonatal hyperbilirubinaemia but if it fails to produce a change of 1-2mg/dl (17-34µmol/L) within 4-6 hours in severe neonatal jaundice, exchange blood transfusion (EBT) is recommended.[6] Other indications for EBT include, serum bilirubin (SB) >20mg/dL (340µmol/L), jaundice to the feet, septicaemia, and clinical signs of bilirubin encephalopathy.[6] It is seldom associated with mortality when closely monitored, however management of hyperbilirubinaemia in resource poor settings like ours remains a challenge with the risk of serious neurologic complications related to bilirubin toxicity and sometimes death. [7]

We have no knowledge of a previous report on the outcome of the treatment of hyperbilirubinaemia in relation to G6PD activity levels in neonates in Jos. This study is aimed at determining the influence of G6PD activity levels on the treatment outcome of hyperbilirubinaemia in jaundice neonates in our SCBUs for improve knowledge and better neonatal management outcome.

METHODOLOGY

Study Area

The study was carried out at the Special Care Baby Units (SCBU) of Jos University Teaching Hospital (JUTH), Bingham University Teaching Hospital (BhUTH), and Plateau State Specialist Hospital (PSSH) in the city of Jos, in North-Central Nigeria. Jos University Teaching Hospital is a 600 bed tertiary hospital with an SCBU of 30 beds capacity, while Bingham University Teaching Hospital

and the Plateau State Specialist Hospital are 250 and 150 bed tertiary hospitals with 15 and 10 bed SCBUs. respectively.[8]

Study Population

Neonates with jaundice admitted into the SCBU of the Jos University Teaching Hospital, Bingham University Teaching Hospital, and the Plateau State Specialist Hospital.

Study Design and Sampling Technique

This study was a cross-sectional study conducted from March 2013 to February 2014. The neonates were recruited using the non-probability convenience sampling technique as they present at the SCBUs with jaundice. They were consecutively enrolled after obtaining parental consent and certified to have met the inclusion criteria. Those whose parents refuse consent, those recently transfused and those with cephalhaematomas, bleeding tendencies and birth asphyxia were excluded. A standardized questionnaire was administered to obtain information on age, weight, and length of the neonate at birth, gestational age at delivery, history of jaundice in siblings and of drugs/chemicals used in pregnancy or after, as well as other risk factors for developing neonatal jaundice. Treatments instituted on admission were noted while outcome was recorded within the study period.

Laboratory Procedures

Samples were collected by the researcher with assistance from the paediatric units' House officers and Registrars. Neonates arms were inspected and antecubital venepuncture done aseptically. Three milliliters of venous blood was taken into an EDTA sample bottle, for full blood count (FBC) using the 3-part Sysmex haematology auto-analyser (KX-21N 2007 model) and was analysed within 6 hours. Reticulocyte count was manually performed using freshly prepared methylene blue as described by Dacie and Lewis.[9] G6PD enzyme activity was determined using the EDTA blood sample with reagents manufactured by the Pointe Reagent Company (USA) with G6PD deficiency defined by enzyme activity < 6.0 IU/gHb.[10] Assay for G6PD activity was mostly carried out within 6 hours but occasionally refrigerated at 2-8°C and analysed within 48 hours. Two milliliter of blood sample was also collected into a plain bottle and analysed immediately for bilirubin assay by the Jendrassik and Grof method using the Roche/Hitachi 902 SN 1694-019-1996 auto analyzer. Where immediate bilirubin assay was not possible, sample were stored at 4°C in a light tight box and assayed within 24 hours of sample collection.

Data Analysis

The data collected was analyzed using EPI-info Version 6 software. Some results were reported in tables, proportions, and percentages. Mean with standard deviation (SD) were used to describe continuous variables while significance between means of two groups was assessed by the student t-test. Non-uniformly distributed continuous variables were reported as median with interquartile (IQR) range and compared using the Kruskal Wallis test. Chi-square was used to compare categorical variables. A *p*-value of <0.05 was considered statistically significant.

Ethical Consideration

Ethical approval was obtained from the Health Research Ethical Committees of the Jos University Teaching Hospital (JUTH), Bingham University Teaching Hospital

(BhUTH), and Plateau State Specialist Hospital (PSSH) Jos. Informed written consent was obtained from the parent or parents of the neonates with no consequence if they choose to decline.

RESULTS

Clinical and Laboratory Parameters of All Subjects and G6PD Status

One hundred and fifty icteric neonates made-up of 92 (61.3%) males and 58 (38.7%) females (M: F= 1.6:1) with a median age at presentation of 3 (Interquartile range-IQR: 1-4) days were studied. One hundred and five (70%) were delivered at full-term gestation (≥37weeks) while 45 (30%) were delivered preterm (<37 weeks). Twenty-nine (19.3%) had history of jaundice in siblings compared to 121 (80.7%) with no such history. Fifty (35.7%) had birth weight of less than 2500g while 90 (64.3%) were of normal birth weight. Birth weight of 10 (6.7%) of the study subjects was unknown because they were delivered at home (Table 1).

All subjects studied had mean haemoglobin and haematocrit concentration of 15.9±2.2g/dL and 0.47±0.06% respectively while the G6PD deficient neonates in this study had a mean haemoglobin concentration of 16.3 ± 2.6g/dL with a haematocrit of 0.47 ± 0.07 (Table 1). Mean values of both the haematocrit and haemoglobin concentration in relation to G6PD activity level showed no statistically significant difference (*p*-value of 0.06 and 0.56 respectively). Mean reticulocyte count for the G6PD deficient neonates was 2.4(IQR: 2-3) % and 2.5(2-3) % for the G6PD normal neonates with no statistically significant difference (*p*-value of 0.67), as shown in Table 1.

Median total serum bilirubin of all the neonates was 204.0(IQR: 168.3-255.5) µmol/L with the median total serum bilirubin concentration of the G6PD deficient icteric neonates being 205.0(IQR: 170.0-281.6) µmol/L.

Table 1. Clinical and Laboratory parameters of all subjects and G6PD status

Parameters	**All Subjects n= 150**	**G6PD deficient n= 61**	**G6PD Normal n= 89**	***P*-value**
Age(days): Median(IQR)	3(1-4)	2(1-4)	3(1-4)	0.52
Sex: n (%)				
Male	92(61.3)	45(73.8)	47(52.8)	0.01
Female	58(38.7)	16(26.2)	42(47.2)	
Duration of Pregnancy(Weeks):				
Full Term: n (%)	105(70.0)	45(73.8)	60(67.4)	0.40
Preterm: n (%)	45(30.0)	16(26.2)	29(32.6)	
History of jaundice in siblings: n (%)	19(12.7)	10(34.5)	19(65.5)	0.45
Birth weight: gm (%)				
<2500	50(35.7)	16(28.1)	34(41.0)	0.12
≥2500	90(64.3)	41(71.9)	49(59.0)	

G6PD activity level: Median(IQR) IU/gHb	7.2(4.6-10.7)	4.0(2.7-4.9)	9.4(7.6-13.6)	
Serum Bilirubin: Median(IQR) µmol/L				
Total Serum Bilirubin	204.0(168.3-255.5)	205.0(170.0-281.6)	200.0(168.0-244.0)	0.14
Unconjugated Bilirubin	184.5(144.5-233.2)	190.4(149.6-261.2)	179.9(144.5-223.0)	0.22
Haemoglobin Conc. g/dL Mean±SD	15.9±2.2	16.3±2.6	15.6±1.9	0.06
Haematocrit Mean±SD	0.47±0.06	0.47±0.07	0.46±0.00	0.56
Reticulocyte Median(IQR)	2.5(2-3)	2.4(2-3)	2.5(2-3)	0.67

G6PD: glucose-6-phosphate dehydrogenase; IQR: interquartile range; RBC: red blood cell

hyperbilirubinaemia with a mean serum bilirubin of 132.3 ± 24.6 µmol/L and 135.8 ± 28.9 µmol/L respectively. Severity of hyperbilirubinaemia in relation to G6PD status did not show any statistical significance with *p*-values of 0.49, 0.78 and 0.28. (Table 2)

Table 2. G6PD status and severity of hyperbilirubinaemia of all subjects

Hyperbilirubinaemia	**G6PD status**							
	Deficient			**Normal**				
	n	**%**	**Mean SB**	**n**	**%**	**Mean SB**	**t**	***p***
Mild	22	36.1	132.3 ± 24.6	40	44.9	135.8 ± 28.9	0.70	0.49
Moderate	24	39.3	205.6 ± 26.6	36	40.4	203.7 ± 24.2	0.29	0.78
Severe	15	24.6	383.1 ± 110.1	13	14.6	338.9 ± 100.4	1.10	0.28
Total	**61**	**100**		**89**	**100**			

SB= Serum bilirubin in µmol/L

G6PD Status and Treatment Modality for Hyperbilirubinaemia in All Subjects

Mode of treatment of hyperbilirubinaemia in 88 (58.7%) of the studied subjects was by phototherapy alone while 62 (41.3%) were treated with phototherapy and exchange blood transfusion (Table 3). Twenty-five (41%) of the neonates with G6PD deficiency were treated with exchange blood transfusion and phototherapy. Thirty-seven (41.6%) of the G6PD normal subjects had exchange blood transfusion and phototherapy. Treatment modality with respect to G6PD status was not

statistically significant (p= 0.94) as shown in Table 3.

Table 3. G6PD status and treatment modality for hyperbilirubinaemia in all subjects

Treatment modality	G6PD status		Total	χ^2	P value
	Deficient n (%)	Normal n (%)			
Phototherapy	36 (59.0)	52 (58.4)	88	0.005	0.94
Phototherapy + EBT	25 (41.0)	37 (41.6)	62		
Total	**61 (100)**	**89 (100)**	**150**		

G6PD Status and Outcome of Treatment for Hyperbilirubinaemia in All Subjects

One hundred and twenty-two (81.3%) of the subjects were discharged home fully recovered, 2 (1.3%) had acute bilirubin encephalopathy, 12 (8.0%) were discharged against medical advice. Fourteen (9.3%) of these neonates died with 5 (8.2%) being G6PD deficient while 9 (10.1%) were G6PD normal. No statistically significant difference was found between the two groups (p- value 0.97) Table 4.

Table 4. G6PD status and outcome of treatment for hyperbilirubinaemia in all subjects

Outcome	G6PD status		Total n (%)*	χ^2	*P*-value
	Deficient n (%)	Normal n (%)			
Normal	50(82.0)	72(80.9)	122(81.3)	0.23	0.97
Encephalopathy	1(1.6)	1(1.1)	2(1.3)		
DAMA	5(8.2)	7(7.9)	12(8.0)		
Died	5(8.2)	9(10.1)	14(9.3)		
Total	**61(61)**	**89(100)**	**150(100.0)**		

DAMA ≡ Discharged against medical advice (%)*= Percentage of column total

DISCUSSION

Prevalence of G6PD deficiency among the icteric neonates in this study was found to be 40.7 % and is comparable to the report from Zaria North West, Nigeria, Ilorin in the North Central region of Nigeria as well as in Egypt and India.[11,12,13,14] These findings are however lower than the prevalence of 62% reported in Ibadan, South West Nigeria.[15] These differences in prevalence may not be unrelated to the report by several geneticists that the varying prevalence of G6PD deficiency in populations is a reflection of adaptation to malarial environments.[15] Cultural and probably religious practices may also be a factor in the differences in prevalence even within the same environment as documented by Cartwright-Jones.[17]

Prevalence of G6PD deficiency among males in this study was 48.9 % while the females had a G6PD deficiency prevalence of 27.5% with an approximate male: female ratio (M: F) of 3:1 similar to a finding in Iraq and some other parts of the World.[18,19] This reaffirmed the natural history of G6PD deficiency being an X-linked recessive disorder, and the fact that male hemizygotes and female homozygotes or hemizygotes as in Turners' syndrome or X-chromosome inactivation are often times affected.[19,20]

The major clinical presentation of these subjects from our laboratory findings was established hyperbilirubinaemia of varying degrees requiring different management protocols. The modalities of management ranged from withdrawing agents identified as icterogenic to antimicrobial therapy, phototherapy and various forms of blood transfusion aimed at reducing morbidity and mortality. Although the frequency of using phototherapy was high in this study, the need for exchange blood transfusion was coincidentally the same for the G6PD deficient and the G6PD normal neonates. Similar findings to this was reported by Frank *et al.* who stated that phototherapy and EBT in G6PD deficient icteric neonates was not significantly higher than in the G6PD normal icteric neonates.[21] This is not surprising as the protocol and modality of the management of icteric neonates is most often based on serum bilirubin levels and not on G6PD activity level. It may also be a reflection of the fact that there was no significant difference in the levels of hyperbilirubinaemia in relation to G6PD status in this study despite other factors like preterm delivery and low birth weight.

This observation differs from the finding by Onyearugha *et al.* in Abakaliki, who reported that phototherapy and EBT were more in G6PD deficient icteric neonates than in other icteric neonates.[22] The finding was based on the fact that apart from the natural immaturity of bilirubin conjugation, G6PD deficiency is associated with even less efficient bilirubin conjugation ability due to its deficiency in the hepatocytes resulting in severe hyperbilirubinaemia.[22] Irrespective of the statistical finding regarding mode of treatment of hyperbilirubinaemia and G6PD status in this study, high rate of EBT was recorded. This might be due to varying indications for EBT like rate of SB rise (> 1mg/dL/hour), clinical signs of bilirubin encephalopathy, concomitant anaemia(<10-12g/dl), septicaemia, SB (in mg/dl) that is ten times baby's weight in kilogram for preterm and low birth weight neonates. This therefore, calls for a viable blood transfusion services in the interim while concerted effort is being made for neonatal screening, early detection of jaundice and treatment using other modes of therapy.

Regarding the possible outcome of treatment for hyperbilirubinaemia in this study, there was no statistically significant difference found in relation to G6PD status. The desire of every physician is to manage and discharge patient possibly in perfect physiologic state and at worst with minimal complications. Frequency of neonates discharged in normal state is relatively encouraging as majority presented within the first three days of life possibly owing to the improved maternal education on neonatal jaundice as well as the fact that G6PD deficiency is not a fatal disorder especially if diagnosed early.[22,23,24]

The finding in this study as related to the development of bilirubin encephalopathy which is associated with kernicterus, agrees with a report from Saudi Arabia and China by Gandapour *et al.* and Loys *et al,* who stated that, whereas neonatal hyperbilirubinaemia were prevalent among G6PD deficient neonates, yet the condition has not been associated with significant kernicterus.[23,24] It is however in contrast to some reports from Sagamu and Zaria, Nigeria where it was demonstrated that G6PD deficiency hyperbilirubinaemia often leads to adverse neurologic events compared to G6PD normal neonates.[25,26] This may reflect genetic mutations specific to different ethnic groups so that in certain populations, hyperbilirubinaemia due to G6PD deficiency results in an increased rate of kernicterus and death when in other populations this has not been observed.[27] It may also be related to the time of presentation and initiation of treatment as well as the presence of other co-morbidities like birth asphyxia and hypoglycaemia affecting the outcome.

Discharge against medical advice (DAMA) is not uncommon in virtually all specialty of medical practice cutting across all age groups. However, a course of concern is when it involves neonates in the event of life threatening emergencies. The finding in our study is comparable with findings from other climes with probably varying reasons.[28] Ibekwe *et al.* reported a relatively lower prevalence in a study in Abakaliki, South Eastern Nigeria while a report in Gujurat, India showed a much higher prevalence of 25.4% with no reason different from the general findings.[29,30] Reasons for DAMA are multifactorial ranging from financial constraint due to parental poverty to hopelessness on disease condition and resort to native treatment especially in developing countries like ours.[30] Therefore, this calls for policy formulation targeted at protecting this vulnerable group of patients as in other developed climes.

Overall neonatal mortality rate in icteric neonates in this study was 9.3% but no statistically significant difference in relation to G6PD status was found. Mortality was however higher amongst the G6PD normal neonates compared to the G6PD deficient neonates. This is not surprising as the cause of death may not be from the hyperbilirubinaemia but from associated disorders of varying severity. Toma *et al.* in a previous study on pattern of neonatal admissions and outcome in Jos reported a frequency of neonatal mortality rate from jaundice of 5.4%.[31]

The mortality frequency in this study can be compared with a reported mortality rate amongst neonates with jaundice in Ilesha, South Western Nigeria and the Niger Delta region respectively.[32,33] However, Ekwochi *et al.* reported a comparatively lower rate of 0.06% in Enugu, South Eastern Nigeria, and this appears to be an aberrant compared to the report from this study and all the other reports.[34] Report from a research in Pakistan also showed a mortality rate of 27 per 1000 live birth.[35]

Most of the studies on neonatal mortality, considered other known causes of neonatal death like prematurity, neonatal sepsis and birth asphyxia in isolation even though they are risk factors for neonatal jaundice.[35] This

may have been responsible for the lower mortality rates from jaundice reported in those studies compared to the finding in our study. It should therefore be noted that while neonatal jaundice can cause neonatal death, it can present with other conditions that are independently major causes of neonatal mortality. This implies that neonates presenting with jaundice should be properly investigated and managed appropriately as G6PD deficiency may not be the only risk factor for hyperbilirubinaemia and its attendant complications or even death.

CONCLUSION

Hyperbilirubinaemia of varying degree with G6PD deficiency as a risk factor is a common reason for neonatal admission in Jos. Severity of hyperbilirubinaemia, its complications and outcome was no different in relation to G6PD status of our subjects but many had to undergo treatments like phototherapy and exchange blood transfusion so early in life despite the attendant complication and side effects of these treatment modalities

REFERENCES

1. Beutler E. Glucose-6-phosphate dehydrogenase deficiency and other red cell enzyme abnormalities. In: Beutler E, Coller B S, Litchman M A, Kipps T J, Seligsohn U (Eds). Williams Hematology 8th edition. New York: McGraw Hill 2000: 647-674.
2. Blann A, Ahmed N. The pathology of Red Blood Cells. In: Andrew Blann, Nasser Amed (Eds). Blood Science: Principles and Pathology 1st Edition. United Kingdom: Wiley Blackwell 2014: 75-107.
3. Olowe SA, Ransome-Kuti O. The risk of jaundice in Glucose-6-phosphate dehydrogenase deficient babies exposed to menthol. *Acta Paediatr Scand* 1980; 64: 341-345.
4. Oduola T, Adeosun G, Ogunyemi E, Adenaike F, Bello A. Studies on Glucose-6-phosphate dehydrogenase stability in blood stored with different anticoagulants. *The Internet J Haematol* 2006; 2: 1-4.
5. Chan M. Neonatal jaundice. In: Stanfield P, Brueton M, Chan M, Parking M, Waterson T (Eds). Diseases of Children in the Subtropics and Tropics 4th edition. London: Arnold, 1991: 221-229.
6. Kristin M, Henry T, Akinbi HT. Neonatal Jaundice: Strategies to reduce bilirubin-induced complications. *Postgrad Med* 1999; 106: 167-178.
7. Lagunju IA, Okafor OO. An analysis of disorders seen at the paediatric neurology clinic, University College Hospital, Ibadan, Nigeria. *West Afr J Med* 2009; **28**: 328-333.
8. Publication of the Directorate of Information, Plateau State Ministry of Information: Census Figures 2006: 1-9.
9. Briggs C, Bain BJ. Basic haematological techniques. In: Bain BJ, Bates I, Laffan MA, Lewis SM (Eds). Practical Haematology 11th edition. London: Churchill Livingstone, 2012: 23-56.
10. Pointe Scientific Incorporation. Glucose-6-Phosphate Dehydrogenase Reagent Set. Procedure Number P803-G7583; 12/09
11. Ahmed H, Yakubu AM, Hendrickse RG. Neonatal Jaundice in Zaria, Nigeria: A Second Prospective Study. *Ann Trop Paediatr* 1995; 1: 15-23.
12. Amiwero CE, Olatunji PO. Prevalence of G6PD Deficiency in Children Presenting with Jaundice in Ilorin, Nigeria. *Int J Biomed & Hlth Sci* 2012; 8: 21-26.
13. Amal AE, Nawal MK, Seham AA, Manal AF, Azza KA. Prevalence of Glucose-6-Phosphate Dehydrogenase Deficiency in Jaundiced Neonates in Egypt. *Aust J of Basic &Appl Sci 2009*; 3: 2016-2023.
14. Pao M, Kulkarn A, Gupta V. Neonatal screening for G6PD Deficiency. *Indian J Paediat* 2005; 72: 835-837.
15. Dawodu AH, Owa JA, Familusi JB. A Prospective Study of the Role of Bacterial Infection and G6PD Deficiency in Severe Neonatal Jaundice in Nigeria. *Trop Geogr Med* 1984; 36: 127-132.

16. Howes ER, Battle KE, Satyagraha AW, Baird JK, Hay SI. G6PD Deficiency: Global Distribution, Genetic Variants, and Primaquine Therapy. *Advances in Parasitology* 2013; 81: 135-169.
17. Cartwright-Jones C. Henna and the Evil Eye, Salt and Demons, and the Geography of G6PD Deficiency. PhD Thesis, Geography Department, Kent State University 2008: 1-20.
18. Al-Hiali SJ. Glucose-6-Phosphate Dehydrogenase Deficiency among Neonates with Hyperbilirubinaemia in Western Iraq. *J Fac Med Baghdad* 2008; 50: 431-434.
19. Jarullah J, Aljaouni S, Sharma MC, Bushra MSJ, Kamal MA. Detection of Glucose-6-phosphate dehydrogenase deficiency in Heterozygous Saudi Female Neonates. *Enz Eng* 2012; 1: 105-107.
20. Veni DVK. The Effect of Gender on Serum Bilirubin Concentration in Infants with Neonatal Hyperbilirubinaemia. *Int J Pharm Bio Sci* 2013; 4: 603-608.
21. Frank JE. Diagnosis and management of Glucose-6-phosphate dehydrogenase deficiency. *Am Fam Physician* 2005; 72: 1277-1282.
22. Onyearugha CN, Onyire BN, Ugboma HAA. Neonatal jaundice: Prevalence and associated factors as seen in Federal Medical Centre Abakaliki, Southeast, Nigeria. *J Clin Med Res* 2011; 3: 40-45.
23. Gandanpur AS, Qureshi F, Mustafa E. Frequency of G6PD Deficiency and related Haemolytic Anaemia in Riyadh, Saudi Arabia. *J Med Coll Abbottabad* 2002; 14: 24-26.
24. Loys L, Chiou SS, Chen BH. G6PD Deficiency in Chinese infants with or without Neonatal Jaundice. *Br J Haematol* 2005; 86: 858-862.
25. Ogunlesi TA, Ogunfowora OB, Ogundeyi MM, Ayeni VA. Jaundice among Hospitalized Newborn Infants in Sagamu: Observations on Aetiology and Clinical Course. *Nig J Paediatr* 2009; 36: 72-79.
26. Duggan MB, Ogala W. Cerebral Palsy in Nigeria- A Report from Zaria. *Ann Trop Paediatr* 1982; 2: 7-11.
27. Kaplan M, Hammerman C. Glucose-6-phosphate Dehydrogenase Deficiency: A Hidden Risk for Kernicterus. *Semin Perinatol* 2004; 28: 356-364.
28. UNICEF. Levels & Trends in Child Mortality: Report 2013-Estimates Developed by the UN Inter-Agency Group for Child Mortality Estimation. Available at https://unicef.org/media/files/2013_IGME_child_mortality_Report.pdf. [Last accessed on March 05,2020]
29. Ibekwe RC, Muoneke VU, Nnebe-Agumadu UH, Amadife MU. Factors Influencing Discharge Against Medical Advice among Paediatric Patients in Abakaliki, South Eastern Nigeria. *J Trop Pediatr* 2009; 55: 39-43.
30. Devpura B, Bhadesia P, Nimbalkar S, Desai S, Phatak A. Discharge against Medical Advice at Neonatal Intensive Care Unit in Gujurat, India. *Inter J Pediatr* 2016; 1-8.
31. Toma BO, Ige OO, Abok II, Onwuanaku C, Abah RO, Donli A. Pattern of Neonatal Admissions and Outcome in a Tertiary Institution in North Central Nigeria. *J Med Trop* 2013; 15: 121-125.
32. Owa JA, Osinaike AI. Neonatal Morbidity and Mortality in Nigeria. *Indian J Pediatr* 1998; 65: 441-449.
33. Ugwu GIM. Pattern of Morbidity and Mortality in Newborn Special Care Unit in a Tertiary Institution in the Niger Delta Region of Nigeria: A Two Year Prospective Study. *Glo Adv Res J Med Sci* 2012; 1: 133-138.
34. Ekwochi U, Ndu IK, Nwokoye IC, Ezenwosu OU, Amadi OF, Osuara D. Pattern of Morbidity and Mortality of Newborns Admitted into Sick and Special Care Unit of Enugu State University Teaching Hospital, Enugu State. *Niger J Clin Pract* 2014; 17: 321-325.
35. Tikmani SS, Warraich HJ, Abbasi F, Rizvi A, Darmstadt GL, Zaidi AKM. Incidence of Neonatal Hyperbilirubinaemia: A Population based Prospective Study in Pakistan. *Trop Med Int Health* 2010; 15: 502-507.