

Glucose-6-Phosphate Dehydrogenase Status in the Term Newborns and Their Clinical and Other Laboratory Correlates.

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Abstract

Background: Glucose-6-phosphate dehydrogenase (G6PD) deficiency is the most common enzyme defect in man. Though G6PD deficiency affects every cell in the body, its primary effects are hematological.

Objectives: The objectives of the study were to determine the G6PD enzyme concentration and deficiency states among the term newborns, to see the impact of the enzyme status with development of neonatal jaundice and to delineate any correlation of the G6PD with other hematological values.

Materials and Method: Total 100 term newborns were enrolled in the study. Umbilical cord blood sample from the placental end were collected for G6PD enzyme assay, blood counts including reticulocyte count, blood indices and bilirubin estimation. Clinical and other relevant data were collected. Statistical analysis was done by using SPSS 19.0 version.

Results: Overall G6PD activity was detected 9.86 ± 1.68 U/g Hb and no G6PD enzyme deficiency state was identified. There were no statistically significant differences in the hematological parameters and cord blood bilirubin concentration between male and females. But females have significantly higher G6PD enzyme concentration than males ($p=0.002$). There were no significant differences in the enzyme concentration in different gestational age groups. There was significant negative correlation between G6PD enzyme and hemoglobin levels, G6PD enzyme concentration with HCT and MCV values.

Conclusion: This study could not identify any G6PD deficiency state. So further large scale community-based study is needed to validate this finding and also establish the normal G6PD enzyme concentration in the population of Bangladesh.

Key Words: Term Newborn, G6PD (Glucose-6-Phosphate Dehydrogenase).

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Introduction

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is the most common enzyme defect in man, being present in more than 400 million people worldwide^{1,2}. G6PD deficiency is an X-linked, genetic defect caused by mutations in the G6PD gene, are associated with a wide range of biochemical and clinical phenotypes³. G6PD is present in all cells; however, its concentration varies in different tissues⁴. In healthy red blood cells, the enzyme operates at only 1% - 2% of its maximum potential: a large reserve of reductive potential exists which is substantially decreased in G6PD-deficient red-blood cells, leading to pathophysiological states⁵.

Data from a series of studies suggest that about a third of all male newborn babies with neonatal jaundice have G6PD deficiency; however, the deficiency is less common in female neonates with jaundice⁶⁻⁸. Jaundice is usually evident by 1 to 4 days of age, similar to physiological jaundice, but is seen at a later time than in blood group alloimmunization (i.e., rhesus incompatibility). Kernicterus, although rare, can produce permanent neurological damage if not promptly managed⁹⁻¹¹. G6PD deficiency and neonatal jaundice vary widely in their frequency and severity in different populations. Where screening for G6PD deficiency is not undertaken routinely, assessment of neonates should be done in those who develop hyperbilirubinemia (bilirubin concentrations greater than the 95th percentile [150 μ mol/L]) within the first 24 h of life, or in those with a history of neonatal jaundice in siblings¹².

The World Health Organization recommends that whenever possible, neonatal screening should be performed on cord-blood samples in populations where G6PD deficiency is common (i.e., where it affects more than 3%-5% of males), to monitor these vulnerable infants for jaundice and institute treatment as early as possible¹³. The highest prevalence is reported in Africa, southern Europe, the Middle East, Southeast Asia, and the central and southern Pacific¹⁴. The prevalence varies from 0-27% in different caste, ethnic and linguistic groups in India¹⁵. In Bangladesh, a cross-sectional study conducted on 90 males, term neonates with jaundice found seven G6PD deficient babies¹⁶.

Objectives:

The objectives of the study were to determine the G6PD enzyme concentration and deficiency states among the term newborns in a tertiary level hospital setting, to see the impact of the enzyme status with development of neonatal jaundice and to delineate any correlation of the G6PD with other hematological values.

Materials and Methods

This was a cross-sectional, analytical study done in the Department of Neonatology and Department of Obstetrics and Gynecology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh from March 2012 to November 2012. All the term newborns delivered during the study period in the Department of Obstetrics and Gynecology, BSMMU were enrolled in this study.

Preterm babies, Rh and ABO incompatibility, Bruises, cephalhematoma, subaponeurotic hemorrhage, infant of diabetic mother, intrauterine growth restriction (IUGR) babies, plethoric newborn suggesting Polycythemia, newborns with congenital malformations, any adverse events in the delivery room were excluded from the study. Ethical approval was taken from the Institutional Review Board (IRB) of BSMMU, Dhaka, Bangladesh. Babies were enrolled as per inclusion and exclusion criteria. Written informed consent was taken from the mothers/parents. Mothers/parents were interviewed at a convenient time before delivery with the help of a pretested structured questionnaire to collect relevant data.

Umbilical cord blood sample were collected from the placental end with the help of a 10 cc disposable syringe. Thereafter, the collected blood was poured into 4 test tubes/vials after removing the needle from the syringe. Two ml of blood for G6PD enzyme assay was poured into an ethylene diamine tetra-acetic acid (EDTA) containing vial supplied by the Armed Forces Institute of Pathology (AFIP) laboratory and shook gently several times to avoid clotting. Another 3 ml of blood was poured into an anticoagulant-containing test tube for blood counts including reticulocyte count and shook well to prevent any clot formation. Remaining portion of blood in the syringe were poured in two separate plain, glass test tube (2 ml in each tube) for blood grouping & Rh typing and estimation of bilirubin concentration.

Cord blood sample collected for blood counts, grouping & Rh typing and bilirubin estimation were sent to the laboratory of Hematology department, BSMMU and the blood samples collected for G6PD enzyme assay were kept in room temperature below 25^oC and sent to the AFIP (Armed Force Institute of Pathology) laboratory within 6 hours of sample collection. For G6PD estimation a commercial kit (BIOREX Diagnostics Limited, UK) was used to measure spectroscopic absorbance at 340 nm due to reduction of NADP⁺ at 37^oC, reflecting G6PD enzyme activity. This kit was used for quantitative determination of G6PD in erythrocytes. The enzyme activity was determined by measurement of the rate of increase in NADPH concentration. The rate of increase in absorbance at 340 nm is the measure of enzyme activity. Hemoglobin (Hb) was measured spectrophotometrically at 540 nm with a commercial kit using the cyanmethemoglobin method [Cell-DYN Ruby, SL. NO. 36130], on the same sample. G6PD activity was recorded as U/g Hb.

Babies who were successfully enrolled in the study, followed-up in the postnatal ward for development of neonatal jaundice and other clinical signs as per study protocol and data were collected accordingly

The data collected during the study procedure included demographic information, maternal medical history, pregnancy history, labor and delivery course, medical status of the newborn, risk factors for hemolysis and hyperbilirubinemia, follow-up for neonatal jaundice, and the need for phototherapy or other treatments. After collection of data mean, median, standard deviation and 95% confidence interval of the G6PD enzyme concentration were calculated. Frequency distribution of study population by G6PD enzyme concentration was plotted. Chi-square test, t-test, ANOVA, Pearson's correlation coefficient test and

other statistical analysis were performed where applicable by using SPSS 19.0 for Windows.

Results

During the study period, umbilical cord blood samples from 100 term newborns were tested for G6PD enzyme concentrations, of whom 47 were males and 53 were females. Thirty-two percent of the newborns were 37 completed weeks of gestation; 29%, 20%, 10% and 9% of them were 38, 39, 40 and 41 completed weeks of gestation respectively. Table-I shows that Mean and SD of birth weight in males and females were 2947 ± 326 and 2921 ± 257 grams, respectively. Mean gestational age of male and female neonates were 38.2 ± 1.25 and 38.4 ± 1.29 weeks, respectively.

Table-I
Demographic characteristics of newborns

Characteristics	Male (n=47)	Female (n=53)	Overall (n=100)	p value
Birth weight, g, mean \pm SD	2947 ± 326	2921 ± 257	2933 ± 290	0.663
Gestational age, weeks, mean \pm SD	38.2 ± 1.25	38.4 ± 1.29	38.4 ± 1.27	0.393
Mode of delivery				
LUCS	45	47	92	0.276
NVD	2	6	8	
Maternal age, years, mean \pm SD	28.34 ± 4.56	27.47 ± 4.59	27.88 ± 4.57	0.346
Parity, no, mean \pm SD	2.38 ± 1.31	2.23 ± 1.22	2.30 ± 1.26	0.538

Table II
G6PD enzyme concentration (U/g Hb)

Sex	Mean	SD	Median	95% CI	P value
Male (n=47)	9.31	1.38	9.2	8.92 – 9.70	0.002
Female (n=53)	10.34	1.79	10.5	9.86 – 10.82	
Overall (n=100)	9.86	1.68	9.65	9.53 – 10.19	

There was no statistically significant difference between male and female neonates in terms of birth weight and gestation. Also, there is no statistically significant difference in the mode of delivery among the study neonates (p value 0.276). Male and female newborns were not also statistically different when their maternal age and pregnancy orders were considered. Table-II shows Mean, SD and 95% CI of G6PD enzyme concentration in male and female newborns which were 9.31 ± 1.38 [8.92 – 9.70] and 10.34 ± 1.79 [9.86 – 10.82] U/g Hb, respectively.

Overall G6PD activity was detected 9.86 ± 1.68 [9.53 – 10.19] U/g Hb. There was significant difference between mean G6PD enzyme activity levels in males and females (p value 0.002). Table-III showing G6PD

enzyme concentrations in different gestational age groups among the term newborns.

Table III
G6PD enzyme concentration in different gestational age groups

Gestation (weeks)	G6PD enzyme concentration (U/g Hb)		
	Mean \pm SD	Median	Min-Max
37	9.69 ± 1.65	9.45	7.0 – 13.5
38	9.62 ± 1.47	9.50	7.5 – 13.0
39	10.35 ± 1.54	10.50	7.8 – 13.0
40	9.48 ± 2.07	8.90	7.3 – 14.3
41	10.57 ± 2.20	9.80	7.9 – 13.6

Table IV*Hematological data and serum bilirubin in the cord blood of male and female term newborns*

Mean \pm SD (median)	Male (n=47)	Female (n=53)	Overall (n=100)	p value
<i>Hemoglobin, g/dL</i>	15.79 \pm 2.25 (16.30)	15.65 \pm 1.76 (15.60)	15.71 \pm 2.00 (15.85)	0.743
<i>RBC Count, 10¹²/L</i>	4.48 \pm 0.73 (4.49)	4.40 \pm 0.55 (4.35)	4.44 \pm 0.63 (4.37)	0.514
<i>HCT, l/l</i>	0.46 \pm 0.07 (0.46)	0.46 \pm 0.05 (0.46)	0.46 \pm 0.06 (0.46)	0.697
<i>MCV, fl</i>	103.2 \pm 7.0 (103.4)	102.2 \pm 14.8 (104.2)	102.6 \pm 11.7 (103.5)	0.684
<i>MCH, pg</i>	35.0 \pm 2.3 (35.0)	35.2 \pm 2.3 (35.4)	35.1 \pm 2.3 (35.1)	0.689
<i>MCHC, g/dL</i>	34.0 \pm 1.4 (33.9)	33.9 \pm 1.2 (33.9)	33.9 \pm 1.3 (33.9)	0.815
<i>Reticulocyte count, %</i>	4.49 \pm 1.09 (4.70)	4.70 \pm 1.10 (4.90)	4.60 \pm 1.09 (4.80)	0.328
<i>Serum Bilirubin, mg/dL</i>	2.03 \pm 0.71 (1.90)	2.15 \pm 0.71 (2.00)	2.09 \pm 0.71 (1.96)	0.405

With ANOVA analysis, there was no significant difference of mean G6PD enzyme concentration between (combined) and within gestational age groups ($p=0.327$). Table-IV shows hematological values and serum bilirubin levels in the cord blood of male and female term newborns. There were no significant sex difference in these laboratory variables.

Table-V shows correlation of G6PD with hematological values and cord blood bilirubin. Highly significant negative correlation between G6PD enzyme and hemoglobin levels was found along with significant negative correlation of G6PD enzyme concentration with HCT and MCV values was also found.

Table V*Correlation of G6PD enzyme concentration with hematological values and serum bilirubin concentration in cord blood*

Hematological Parameter	Pearson (r) Correlation	p Value
<i>Hemoglobin</i>	- 0.314**	0.001**
<i>RBC count</i>	- 0.187	0.062
<i>HCT</i>	- 0.208*	0.038*
<i>MCV</i>	- 0.200*	0.046*
<i>MCH</i>	- 0.091	0.371
<i>MCHC</i>	- 0.187	0.062
<i>Reticulocyte count</i>	0.009	0.927
<i>Serum bilirubin</i>	0.065	0.520

** Correlation is significant at the 0.01 level (2-tailed)

* Correlation is significant at the 0.05 level (2-tailed)

Mean serum bilirubin concentration in the cord blood of the study subjects was (2.09 \pm 0.71) with no significant difference among male and female term newborns ($p=0.405$). Also there was insignificant correlation of G6PD enzyme and serum bilirubin concentrations in the cord blood ($r=0.065$, $p=0.520$). None of the term newborns developed neonatal jaundice that required interventions in the form of phototherapy or exchange transfusion.

Discussion

Present study was conducted to determine the G6PD enzyme status in the term newborns and to compare the G6PD enzyme concentration, hematological values and serum bilirubin concentration among male and female term newborns on cord blood samples. There were no significant differences in birth weight, gestation age, mode of delivery, maternal age and parity among male and female newborns. Though there was statistically significant difference in G6PD activity among male and female neonates, no G6PD-deficient newborn was identified in this study. Riskin A et al found 95.5% of the newborns had G6PD activity within the normal range (>7.0 U/g Hb), 2.7% were G6PD-deficient (G6PD <2.0 U/g Hb), and 1.8% had borderline G6PD activity (2-7 U/g Hb). Males were predominant in the G6PD-deficient group. There was no significant difference among the groups in terms of birth weight and gestational age¹⁷.

Frequency distribution of study population by G6PD enzyme concentration was well-matched with the similar analysis done by Algur N et al¹⁸ with few exceptions: (1) in the present study, the deficient distribution was missing as no G6PD-deficient male or female newborns were identified and (2) possible

female heterozygotes were also absent. In this study, male G6PD-deficient group was missing as no value was detected <7.0 U/g Hb and only G6PD-normal male, presumably hemizygotes were found. No female term newborns were identified with lower enzyme value those can be categorized into probable genotypes such as presumed deficient homozygotes or presumed heterozygotes as described by Algur et al¹⁸.

In this study, G6PD enzyme concentrations were found (9.31 ±1.38) and (10.34 ±1.79) U/g Hb in male and female term newborns, respectively. The enzyme concentrations in male neonates were significantly lower than their female counterparts. A similar study in Nigeria, described that normal G6PD enzyme concentration in female babies were significantly higher than that in male babies (5.72 ±2.45 U/g Hb versus 4.99 ±2.3 U/g Hb, p = 0.002).¹⁹ The gene for the G6PD enzyme is located on the X chromosome and so, because the female is doubly endowed, she should demonstrate higher enzyme levels. In contrast to the above studies, another study conducted in Isfahan, Iran found that the mean G6PD activities were not significantly different between males and females in G6PD deficient subjects (male 3.17±1.74, female 3.49±2.17; p=0.45) and in G6PD normal group (male 34.94±12.04, female 35.31±11.96; p=0.58).²⁰ Ainoon et al²¹ also showed that there were no significant differences in the mean G6PD activity between sexes within and between two racial groups (669 Malays, 307 Chinese).

In the present study, overall mean G6PD activity was 9.86 ±1.68 U/g Hb. In a study in Bangladesh Sultana et al²² found that mean G6PD enzyme level was 6.69 ± 1.19 (range 5.00 –9.60) U/g Hb in 5-40 year old healthy subjects. These findings are consistent with the notion that term neonates at birth have higher G6PD activity than adults.²³⁻²⁶ Mohrenweiser et al²⁷ found that newborns had higher G6PD activity than adults. Additional as yet undetermined factors appear to be responsible for the intrinsically higher G6PD activity in neonates.²⁸

In the present study, mean Hb concentration in the newborns having jaundice was 15.71±2.00 g/dL and there was no statistically significant difference between male and female newborns (p=0.743) though their G6PD enzyme concentrations had significant differences. These findings support the postulation of the mechanism of neonatal jaundice in G6PD deficiency other than hemolysis.²⁹

In a study conducted in Bangladesh, Akter et al³⁰ showed that hemoglobin concentration, hematocrit, total count of red blood cell and reticulocyte count showed non-significant positive correlations (r=0.745, r=0.205, r=0.329, r=0.104) with erythrocyte G6PD level in deficient neonates. But in the present study, there was highly significant negative correlation between G6PD enzyme and hemoglobin levels (r= -0.314, p=0.001). There was also significant negative correlation among G6PD enzyme activity and hematocrit (r= -0.208, p=0.038) and MCV values (r= -0.2, p=0.046). Surprisingly, this was a new finding in the context of G6PD enzyme activity and hematological findings. The correlation between G6PD enzyme and hematological indices may be different in G6PD-normal and G6PD-deficient newborns. This negative correlation may not be related to G6PD enzyme concentration. Factors other than G6PD enzyme may be responsible for this relationship.

Conclusion

This small scale, tertiary level hospital-based study could not identify any G6PD-deficient term newborns but has brought about some interesting findings, particularly a significant negative correlation between G6PD enzyme concentration and hemoglobin, hematocrit and MCV of RBC in a limited sample of G6PD-normal term newborns which can be a very exciting area of further research in the countries where G6PD deficiency state is not prevalent and globally.

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