

## Prevalence of Glucose-6-phosphate Dehydrogenase Deficiency in Jaundiced Neonates in Egypt

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**Abstract:** Glucose-6-phosphate dehydrogenase deficiency is the most common inherited metabolic disorder and clinically significant red cell enzyme defect in man. Beside favism, drug-or infection induced hemolysis and chronic non spherocytic hemolytic anemia. Severe neonatal jaundice proved to be the most common clinical manifestation and a globally important, most dangerous consequence of glucose-6-phosphate dehydrogenase (G6PD) deficiency. So the early characterization of G6PD activity provides an etiological diagnosis for neonatal jaundice (NJ), as well as the opportunity to give the newborn's family information concerning hemolytic crisis prevention. Aim: this present study was conducted in an attempt to evaluate the prevalence of G6PD deficiency in relation to neonatal hyperbilirubinemia in Egyptian infants. Subjects and methods: the study included 53 infants presenting with neonatal jaundice 40 males (75.5%) and 13 females (24.5%) with a ratio 3:1. All infants of the study were subjected to complete history taking, thorough physical examination and the following laboratory investigation: routine hematological evaluation, total and direct serum bilirubin levels, direct coomb's test and we performed qualitative and quantitative red blood cells glucose-6-phosphate dehydrogenase assay in all cases. Results: The study revealed that 16/53 cases (30.2%) were G6PD deficient. In the G6PD deficient cases no evidence of other factors known to cause hyperbilirubinemia were detected. Out of the 16 G6PD deficient cases 12 cases (75%) were males and 4 cases (25%) were females with a male to female ratio 3:1 and 4 cases (25%) were markedly G6PD enzyme deficient and 12 cases (75%) were moderately G6PD enzyme deficient. The incidence of G6PD def. was significantly higher (66.7%) among the preterm infants compared to the frequency of (25.5%) among the full term infants ( $P=0.04$ ). There was a significant difference between G6PD deficient cases and G6PD normal cases as regards total peak serum bilirubin ( $22.26\pm 8.36$ ,  $18.14\pm 3.82$  respectively) ( $P=0.001$ ). On the other hand, hematological indices failed to show evidence of frank hemolysis as the hemoglobin levels, hematocrite values, reticulocytic count and percentage of anemia did not significantly differ between G6PD deficient and G6PD normal cases. Out of the 16 G6PD deficient cases 3 cases (18.8%) developed kernicterus compared to one case (2.7%) among G6PD normal cases which was statistically significant ( $P=0.04$ ). On the other hand there was no significant difference between G6PD deficient and G6PD normal cases as regards frequency of using phototherapy, duration of its application ( $3.9\pm 1.2$ ,  $2.85\pm 0.56$  respectively) and the need for exchange transfusion ( $P>0.05$ ). Infants with marked G6PD deficiency were not significantly different from cases with moderate G6PD deficiency as regards sex distribution, hematological indices, time of appearance of jaundice, duration of phototherapy and the need for exchange transfusion. Conclusion: the incidence of glucose-6-phosphate dehydrogenase deficiency in jaundiced infants was high in this study this signifies the role of G6PD deficiency in developing NJ among Egyptian infants. So early neonatal screening programmes should be instituted in countries where the deficiency is prevalent.

**Key words:** Glucose-6-phosphate dehydrogenase deficiency, Neonatal hyperbilirubinemia, Kernicterus.

### INTRODUCTION

Glucose-6-phosphate dehydrogenase is an x-linked inherited disorder most commonly affects people of African, Asia, Mediterranean or Middle-Eastern descent (*Kaplan et al., 2009*). Approximately 400 million people are affected worldwide. Homozygotes and heterozygotes can be symptomatic, although the disease typically is more severe in person who is homozygous.

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Glucose-6-phosphate dehydrogenase deficiency causes a spectrum of diseases including neonatal hyperbilirubinemia, acute hemolytic anemia and severe chronic non-spherocytic anemia. None hemolytic sequelae have been claimed as well (*Iranqour et al., 2003*). Also G6PD def. increases the vulnerability of erythrocytes, to oxidative stress (*Atay et al., 2006*). Despite definite association between G6PD def. and neonatal jaundice reported repeatedly and independently in numerous studies of many countries especially within the geographic distribution of the Mediterranean type of the enzyme defect, the mechanism by which G6PD def. causes neonatal hyperbilirubinemia is not completely understood (*Dors et al., 2008*). Although hemolysis may be observed in neonates who have G6PD deficiency and are jaundiced, other mechanisms appear to play a more important role in the development of hyperbilirubinemia, as hyperbilirubinemia is secondary to impairment of bilirubin conjugation and clearance by liver cells (*Kaplan et al., 2007*).

***Aim of Work:***

To determine the prevalence of G6PD deficiency in relation to neonatal hyperbilirubinemia in Egyptian infants.

**MATERIALS AND METHODS**

This study included 53 infants with neonatal hyperbilirubinemia 40 males (75.5%) and 13 females (24.5%). All patients were out patients i.e., admitted from home or discharged from hospital and readmitted.

N.B: for purpose of this study neonatal jaundice was defined by a peak serum bilirubin level of > or = 15 mg/dl.

All cases of the study were subjected to:

- Full history taking.
- Physical examination.
- Diagnostic laboratory investigations including:
  - Direct coomb's test to exclude cases of isoimmune hemolysis.
  - Routine hematological evaluation.
  - Total and direct serum bilirubin levels.
- Detecting of glucose-6-phosphate dehydrogenase activity:
  - All cases of the study were screened for G6PD def. by a "qualitative" enzyme assay using the methemoglobin reduction test (*Sampavat et al., 2001*).
  - Quantitation of G6PD def. in erythrocytes by a "quantitative" kinetic assay was carried out only if G6PD deficiency was provisionally diagnosed by qualitative assay. Samples were taken and enzyme activity was determined by measuring the rate of absorbance change at 340 nm, due to reduction of NADP to NADPH when a sample was incubated with G6PD. Glucose-6-phosphate dehydrogenase activity was calculated in relation to erythrocyte count. Commercially available kits (Cat. No. 038T, United Diagnostic Industry Dammam, Kingdom of Saudia Arabia) were used.

Results were interpreted as the percentage of normal G6PD activity. Enzyme activity less than 10% of the lower limit of normal activity was classified as severe deficiency whereas the activity between 10 and 60% was classified as mild to moderate deficiency. Reference range according to manufacturer was 120-240 nm/RBC in million (*Ainoon et al., 2003*).

***Statistical Analysis:***

SPSS for windows version 7.0 computer program was used for statistically analysis. Ap value less than < 0.05 was considered significant and < 0.001 was considered highly significant. The T-test used to compare between two independent means.

**RESULTS AND DISCUSSION**

***Results:***

A total number of 53 cases with neonatal jaundice were studied 40 males and 13 females with a male to female rates, 3:1.

Total serum bilirubin levels was highly significantly higher in G6PD deficient cases than in G6PD normal cases (P=0.001). Also frequency distribution of kernicterus was significantly higher in G6PD deficient cases than in G6PD normal cases (P=0.04).

**Table 1:** Clinical laboratory finding of cases.

Parameters	n=53	
Sex		
Male	40	75.5%
Female	13	24.5%
Gestational age		
Full-term	47	88.7%
Preterm	6	11.3%
Consanguinity	17	32%
Mode of laboratory		
NVD	30	56.6%
CS	23	43.4%
% of anemia according to age	34	64.1%
Glucose-6-phosphate dehydrogenase deficiency		
Total	16/53	30.2%
Male	12/16	75%
Female	4/16	25%

**Table 2:** Clinical and laboratory findings in G6PD deficient versus G6PD normal cases.

Parameters	G6PD deficient cases n=16		G6PD normal cases n=37		P-value
Sex					
Male	12	75%	27	72.9%	NS
Female	4	25%	10	27%	NS
Consanguinity	7	43.7%	10	27%	NS
Previous history of NJ	3	18.7%	7	18.9%	NS
Gestational age					
Full-term	12	75%	35	94.6%	
Pre-term	4	25%	2	5.4%	0.04
Birth weight (Kgs)	3.01±0.70		2.89±0.61		NS
Appearance of jaundice (days)	3.35±1.65		3.23±1.34		NS
Icteric agents	6	37.5%	8	21.7%	NS
Kernicterus	3	18.8%	1	2.7%	0.04
% of anemia according to age	8	50%	26	70.2%	NS
Total peak serum bilirubin (mg/dl)	22.26±8.36		18.14±3.82		0.001
Indirect bilirubin (mg/dl)	23.3±6.36		21.10±5.45		NS
Direct bilirubin (mg/dl)	28.34±6.59		25.81±6.12		NS
HB (gm/dl)	13.52±4.54		12.91±3.15		NS
HCT (Ratio)	40.6±13.0		39.0±9.70		NS
Reticulocytes	2.66±1.65		1.85±1.45		NS
N: of cases receiving phototherapy	16	100%	36	97.2%	NS
Duration of phototherapy	5.02±1.93		3.76±1.40		NS
Exchange transfusion	10	62.5%	15	40.5%	NS

NJ= Neonatal jaundice; HB= Hemoglobin; HT= Hematocrite value; NS = Not significant

**Table 3:** Clinical and laboratory findings in marked G6PD deficient cases versus moderate G6PD deficient cases.

Parameters	Marked deficient		Moderately deficient		P-value
Sex					
Male	3	75%	9	75%	
Female	1	25%	3	25%	NS
Gestational age					
Full-term	3	75%	9	75%	
Pre-term	1	25%	3	25%	NS
Appearance of jaundice (days)	4.50±2.31		3.37±1.09		NS
Kernicterus	1	25%	2	16.6%	NS
Total peak serum bilirubin (mg/dl)	46.65±7.81		24.81±6.95		NS
Indirect bilirubin (mg/dl)	24.55±7.31		22.7±6.15		NS
Direct bilirubin (mg/dl)	1.95±1.25		2.16±1.35		NS
HB (gm/dl)	12.85±1.98		14.06±5.22		NS
HCT (Ratio)	35.82±8.41		41.45±15.01		NS
Reticulocytes	2.84±2.05		2.98±2.05		NS
% of anemia according to age	3	75%	5	41.6%	NS
Duration of phototherapy	3.9±1.20		2.85±0.56		NS
Exchange transfusion	3	75%	7	58.3%	NS

The comparison between two groups revealed no significant differences regards sex distribution, gestational age, time of appearance of jaundice, bilirubin levels, laboratory parameters, duration of phototherapy and number of cases requiring exchange transfusion.

As G6PD deficiency was significantly higher among the group of preterm infants (66.7%) compared to (25.5%) among the full-term infants ( $P=0.04$ ), and the frequency distribution of preterm was significantly higher within G6PD deficient group (25%) compared to (5.4%) in the non-deficient group.

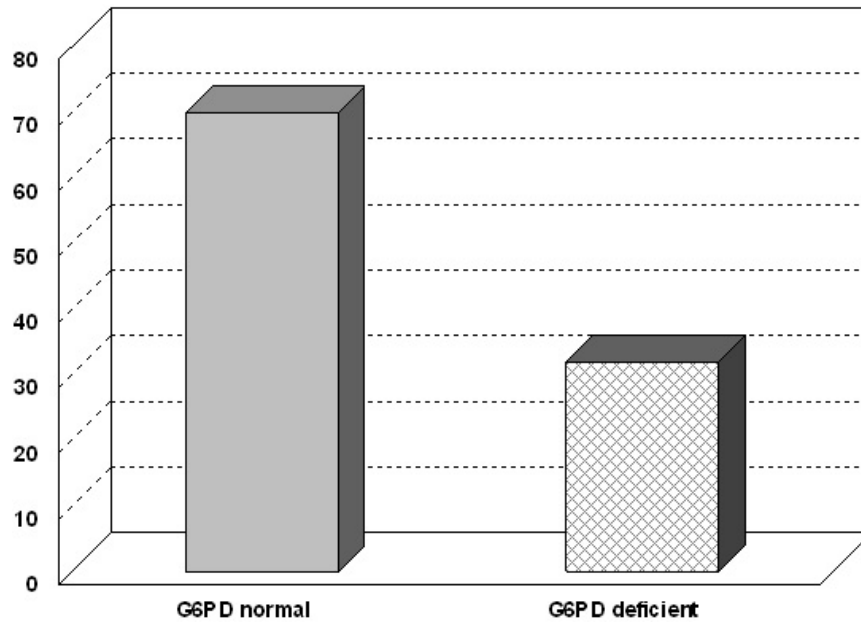


Fig. 1: Incidence of G6PD deficiency among the studied cases.

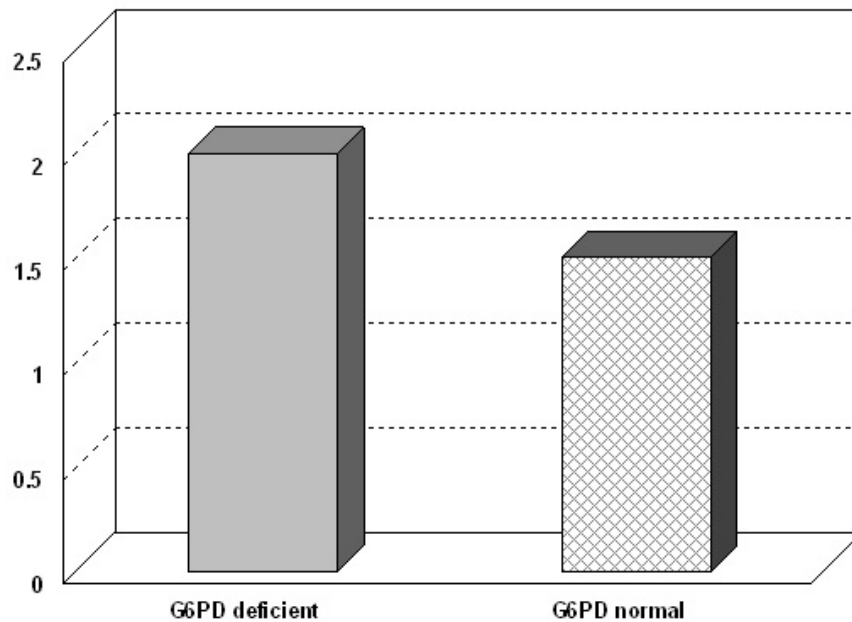
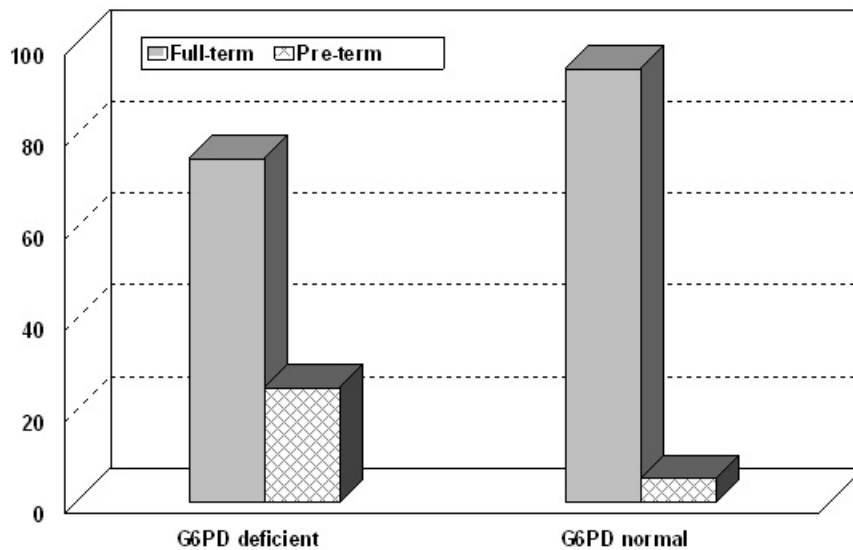


Fig. 2: Total serum bilirubin levels in G6PD deficient cases versus G6PD normal cases.

**Discussion:**

Glucose-6-phosphate dehydrogenase deficiency is the most common enzyme deficiency world wide. It is an x-linked recessive disorder expressed mostly in males. G6PD def. causes a spectrum of diseases including neonatal hyperbilirubinemia, acute hemolysis and chronic hemolysis (Dors et al., 2008). It occurs with increased frequency throughout Africa, Asia, the Mediterranean Middle East (Jennifer et al., 2005). As Egypt lies in a special geographic situation at the meeting of the three continents with different ethnic groups the incidence of G6PD def. varies widely in different localities. Genetic heterogeneity has been discovered in different Mediterranean populations. As many as 19 variants were found in Egypt still the Mediterranean



**Fig. 3:** Gestational age among G6PD-deficient versus G6PD-normal cases.

variant of the enzyme deficiency is considered the most prevalent in Egypt (*Kamal et al., 1967*). The high rate of consanguineous marriage in some populations may well have influenced the genetic make up and resulted in the propagation of such deleterious genes (*Cuppellini et al., 2008*).

In this study the incidence of G6PD def. was 16/53 (30.2%) among 53 cases of neonatal jaundice. This result is very near to those of several studies conducted in India where G6PD def. accounted 32% of the cases presenting with neonatal hyperbilirubinemia (*Pao et al., 2005*). Also G6PD def. was found in 38.2% of the hyperbilirubenemic neonates in Nigeria (*Uko et al., 2003*). Several other studies from Saudia (*Niazi et al., 1996 and Muzaffer et al., 2005*). Iran (*Iranpour et al., 2008*), Jamica (*Gibbs et al., 1997*) and Chinese (*Loys et al., 2005*) reported that G6PD def. is strongly associated with NJ and even kernicterus. G6PD def. is also considered as one of the most common causes of NJ among infants in Greece (*Missiou et al., 1992*), Singapore (*Koosho et al., 2007*) and Taiwan (*Chiang et al., 1999*).

However, because not all G6PD deficient infants become jaundiced and due to the marked variation in the incidence and intensity of G6PD deficiency associated neonatal jaundice among various populations, there has been an active search for additional factors that may cause neonatal jaundice when combined with G6PD deficiency. Additional genetic factors e.g., genetically determined variation in bilirubin elimination, a transient developmentally-related enzyme deficiency could explain ethnic differences in the incidence of neonatal jaundice in G6PD deficient infant in various population (*Kaplan et al., 2007*).

As regards sex prevalence in the present study out of 16 G6PD deficient cases 12 (75%) were males and 4 (25%) were females with a male to female ratio 3:1. The same ratio of 3:1 was found in a study done in India (*Iranqour et al., 2003*) on 53 cases with G6PD def. associated with NJ. This non significant difference between males and females within the prevalence of G6PD def. of the jaundiced infants of the present study goes in agreement with previous studies done by (*Sampavat et al., 2001 and Weng et al., 2003*).

The marked expression of G6PD deficiency gene in the liver of heterozygous females as well as the variation in the proportion of G6PD deficiency in cells in heterozygous females, some having normal red cell activity, whereas other having a quantitative deficiency as severe as hemizygotes probably explain the relatively higher than expected frequency of G6PD def. in jaundiced females (*Edwards, 2002*). In contrast a significant association between G6PD def. and neonatal jaundice was observed in males but not in females neonates in Taiwan (*Chiang et al., 1999*). Other studies also declared that males with G6PD deficiency may be inherently more vulnerable to NJ than females but the reason for this gender differences remains to be elucidated (*Weng et al., 2003*). Unidentified environmental or exogenous factors exposing the infants to oxidant injury such as infection or the application of dyes or powder to the umbilicus may also play a role in the prevalence of NJ associated with G6PD def. (*Beutler, 1994*).

In this study these potentially hemolytic factors were only excluded by history taking as out of the 16 G6PD def. cases (37.5%) gave history of exposure to icterogenic agents e.g., sulpha powder applied to the umbilicus. This frequency was not significantly different when compared to G6PD normal infants (24.3%). This agrees with other reports from different countries who have documented that neonatal hyperbilirubinemia were significantly more prevalent among G6PD def. infants compared to G6PD normal infants often with no

apparent cause or offending factor and even when all known triggers of hemolysis have been eliminated, the authors concluded that the role of such hemolytic agents is doubtful (*Jallohs et al., 2005 and Ahmadi et al., 2008*). So, G6PD def. acts as an independent icterogenic factor and as such will increase the proportion of infants developing significant NJ in the absence of other causes of NJ in comparison to the same proportion among the G6PD normal infants of the same population (*Valaes; 1997 and Holty et al., 2007*).

In contrast, a number of studies conducted over Nigeria infants declared a direct association between exposure to icterogenic agents and severe NJ and kernicterus in G6PD deficient infants (*Owa, 1989*).

As regards gestational age, the frequency distribution of preterm was significantly higher within G6PD deficient group (25%) compared to the non deficient group (5.4%). There was also a significant higher incidence of G6PD def. within the preterm infants of (66.7%) compared to the frequency of (25.5%) among the full-term infants ( $P=0.04$ ). This agrees with previous studies that declared a statistically significant inverse relationship between the percentage of G6PD def. and gestational age in NJ (*Keplan et al., 2005 and Costa et al., 2008*). This may be explained by a transient state of immaturity and or instability of the enzyme particularly evident in the preterm jaundiced infants (*Bender et al., 2007*).

In the present study, total peak serum bilirubin levels was significantly higher among G6PD deficient group compared to non deficient group ( $P=0.001$ ). In agreement with the present results, several studies reported that the maximal total serum bilirubin levels were significantly higher among G6PD deficient jaundiced neonates when compared with G6PD normal icteric neonates (*Iranqour et al., 2003; Abolghasemi et al., 2004; Kaplan et al., 2004 and Atay et al., 2006*).

In the present study, out of the 16 G6PD deficient cases 3 cases developed kernicterus (18.7%) compared to one case in the G6PD normal group (2.7%) which was significantly different ( $P=0.04$ ). This agrees with study performed in Greece where an incidence of kernicterus of as much as 30% in enzyme deficient infants was reported (*Missiou-Tsagaraki, 1992*).

In recent report on the united states based pilot kernicterus registry G6PD, deficiency was shown to affect 31.5% of 61 patients with kernicterus (*Burke et al., 2009*). Also previous study in South East reported that 55% of G6PD deficient jaundiced cases developed kernicterus (*Katars, 2007*) and in Basrah phototherapy did not reduced the need for exchange transfusion which was necessary in 28.4% of the G6PD deficient infants and 8.4% developed kernicterus and one died (*Al-Noama et al., 1987*).

In contrast, other studies in Arabia and Chinese patients reported that whereas neonatal hyperbilirubinemia and the use phototherapy were more prevalent among the G6PD def. neonates yet the condition has not been associated with kernicterus (*Gandapour et al., 2002 and Loys et al., 2005*). So in certain populations hyperbilirubinemia secondary to G6PD deficiency results in an increased rate of kernicterus and death whereas in other population this has not been observed. This may reflect genetic mutations specific to different ethnic groups (*Kaplan et al., 2004*).

In this study comparing G6PD deficient cases with G6PD normal cases and cases with marked G6PD deficiency with cases with moderate G6PD deficiency as regards hemoglobin levels, hematocrite values, reticulocytic count and percentage of anemia for age revealed no significant difference ( $P>0.05$ ). So hematological indices failed to show evidence of frank hemolysis is between two groups of G6PD deficient and G6PD normal cases and between marked G6PD deficient cases and moderate G6PD def. cases. These results are consistent with several studies based on hematological indices that could not demonstrate evidence of acute hemolysis in G6PD deficient jaundiced cases (*Jennifer et al., 2005*). Also measuring ETCO (End-Tidal carbon monoxide) recently concluded that marked hemolysis and increased bilirubin production in G6PD deficient Mediterranean type is not sufficient to explain hyperbilirubinemia and they reported that hemolysis is not a main determinate of neonatal jaundice in G6PD def. babies (*Jallohs et al., 2005*).

Although in the present study the frequency of using phototherapy was high and the duration of its application relatively long and the need for exchange transfusion appeared to be more within the G6PD-deficient jaundiced neonates still the G6PD deficient group did not show significant differences within these aspects when compared with non deficient group. Also the duration of phototherapy and frequency of exchange transfusion were not significantly different in group of marked G6PD def. when compared to the group of moderate deficiency ( $P\text{-value} > 0.05$ ) these results agree with *Jennifer et al. (2005) and Atay et al., (2006)* who reported that the use of phototherapy and exchange transfusion in G6PD deficient icteric neonates was not significantly higher than in G6PD normal icteric neonates. In contrast other studies reported that phototherapy and exchange transfusion were required more prevalent in G6PD deficient jaundiced neonates than in other icteric neonates (*Iranpour et al., 2003 and Kaplan et al., 2004*). Also in Greece approximately 30% of all exchange transfusion for hyperbilirubinemia were done in G6PD deficient infants (*Missiou-Tasagaraki, 1992*).

The mechanism by which G6PD deficiency may predispose to hyperbilirubinemia and the pathophysiologic basis for excessive jaundice in infants with G6PD deficient has not been established (*Weng et al., 2003*). The absence of frank anemia and other changes supportive of acute hemolysis in G6PD deficient infants with NJ

(as documented in the present study) direct attention away from red cells toward a hepatic origins. Defective G6PD activity in the hepatocyte was suggested as an alternative factor playing a role in the pathogenesis of G6PD deficiency related NJ (*Jallohs et al., 2005*).

An interaction between G6PD deficiency and promoter polymorphism for the gene encoding the bilirubin conjugation enzyme has been implicated in the pathogenesis of hyperbilirubinemia in G6PD deficient infants. Also decrease bilirubin elimination in hepatocytes play a major role (*Kaplan et al., 2009 and Edwards et al., 2002*).

#### **Conclusion:**

Since glucose-6-phosphate dehydrogenase seems to be a relatively common cause of neonatal jaundice in Egyptian infants early detection of this enzymopathy by cord blood screening and monitoring for possible jaundice are recommended in at least preterm infants.

Also screening for G6PD def. is recommended in any neonate presenting with jaundice regardless of sex not only to define the etiology of hyperbilirubinemia but also to give the newborn's family information concerning hemolytic crisis prevention.

Among practicing physicians a high order of awareness about the possibility of G6PD deficiency is necessary when managing neonates with unexplained hyperbilirubinemia.

#### **Abbreviations:**

-*G6PD def*: Glucose-6-phosphate dehydrogenase deficiency.

-*NJ*: Neonatal jaundice.

-*HB*: Hemoglobin.

-*NADP*: Nicotinamide adenine dinucleotide phosphate.

-*NADPH*: Reduced form of NADP.

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