Rate of glucose-6-phosphate dehydrogenase deficiency in neonatal indirect hyperbilirubinemia at a private tertiary centre

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ABSTRACT

الأهداف: دراسة معدل حديثي الولادة في المستشفى الذين يعانون من نقص هيدروجيناز الجلوكوز 6 فوسفات (G6PD) والذين يعانون من فرط بيليروبين الدم غير المباشر في مركز الرعاية الثالثية الخاص في الأحساء، المملكة العربية السعودية، على مدى 4 سنوات ومقارنة خصائص نقص إنزيم G6PD وخصائصهم. حديثي الولادة الطبيعيين الذين تم إدخالهم لفرط بيليروبين الدم غير المباشر.

المنهجية: أجريت دراسة الحالات والشواهد بأثر رجعي في مستشفى الموسى التخصصي، الأحساء، المملكة العربية السعودية. تم جمع البيانات من نظام ياساسي الطبي في الفترة من 2018 إلى 2021 وتم الانتهاء منها في عام 2024. وتضمنت الدراسة مجموعتين: حديثي الولادة الذين يعانون من نقص G6PD الطبيعي والذين يعانون من نقص G6PD والذين يعانون من فرط بيليروبين الدم غير المباشر وليس لديهم مسببات معروفة لانحلال الدم. ركز التحليل على مستويات البيليروبين في الدم، ومستويات البيليروبين المباشر، ومستويات الهيماتوكريت، ومستويات الهيموجلوبين، ونسبة الخلايا الشبكية، ومستويات G6PD، ومدة العلاج الضوئي، والحاجة إلى تبادل نقل الدم.

النتائج: شملت الدراسة 3200 طفل حديث الولادة مصابين بفرط بيليروبين الدم، منهم 274 طفلاً يستوفون معايير الاشتمال. كان هناك ما مجموعه 103 (37.6%) من الولدان يعانون من نقص إنزيم G6PD، منهم 77 (74.8%) ذكور و 26 (25.2%) إناث. أظهر الولدان الذين يعانون من نقص هيدروجيناز الجلوكوز 6 فوسفات مستويات أعلى بكثير من إجمالي البيليروبين الأولي وأوقات أخذ العينات السابقة. لم يكن هناك ارتباط مهم بين نقص إنزيم G6PD ومستويات الهيماتوكريت أو الهيموجلوبين عند الولدان المصابين بفرط بيليروبين الدم، لكن 4 حديثين احتاجوا إلى تبادل الدم، مما يدل على دلالة إحصائية (p=0.009).

الخلاصة: ارتفاع معدل نقص إنزيم G6PD عند الولدان المصابين بفرط بيليروبين الدم غير المباشر، مما يتطلب مراقبة دقيقة لمنع عمليات نقل الدم، مع عدم وجود آثار ملحوظة.

Objectives: To investigate the rate of hospitalized neonates with glucose-6-phosphate dehydrogenase (G6PD) deficiency presented with indirect hyperbilirubinemia at a private tertiary center in Al-Ahsa, Saudi Arabia, over 4 years and to compare the characteristics of G6PD-deficient and normal neonates admitted for indirect hyperbilirubinemia.

Methods: The retrospective case control study was carried out at Almoosa Specialist Hospital, Al-Ahsa, Saudi Arabia. Data were collected from Yassasi Medical System from 2018-2021 and finalized in 2024. The study included 2 groups: G6PD-normal and G6PD-deficient neonates with indirect hyperbilirubinemia not having recognizable triggers of hemolysis. The analysis focused on serum bilirubin levels, direct bilirubin levels, hematocrit levels, hemoglobin levels, reticulocyte percentage, G6PD levels, duration of phototherapy, and the need for exchange transfusion.

Results: The study enrolled 3200 neonates with hyperbilirubinemia, of whom 274 met inclusion criteria. A total of 103 (37.6%) neonates were G6PD-deficient, with 77 (74.8%) being male and 26 (25.2%) female. Glucose-6-phosphate dehydrogenase-deficient neonates exhibited significantly higher initial total bilirubin levels and earlier sampling times. There was no significant correlation between G6PD deficiency and hematocrit or hemoglobin levels in hyperbilirubinemic neonates, but 4 neonates required exchange transfusion, demonstrating statistical significance (p=0.009).

Conclusion: High rate of G6PD deficiency in neonates with indirect hyperbilirubinemia, requiring close monitoring to prevent exchange transfusions, with no significant differences in hematocrit or hemoglobin levels.

Keywords: glucose phosphate dehydrogenase, deficiency, neonatal, hyperbilirubinemia, phototherapy, transfusion

Saudi Med J 2024; Vol. 45 (10): 1057-1063
doi: 10.15537/smj.2024.45.10.20240524

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Received 18th June 2024. Accepted 2nd September 2024.

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Glucose-6-phosphate dehydrogenase (G6PD) is the primary source of energy from glucose for erythrocytes.[1] This enzyme generates reduced glutathione phosphate and reduced nicotinamide adenine dinucleotide phosphate, crucial for protecting erythrocytes against oxidative damage. Glucose-6-phosphate dehydrogenase deficiency is an enzymopathological disorder induced by mutations in the X-linked gene. Consequently, G6PD deficiency is predominantly reported in males.[2] It ranks among the most prevalent enzymatic disorders across the world, affecting over 400 million people.[3] The G6PD deficiency is highly prevalent in Mediterranean, Asian, and African populations. In the Middle East, its prevalence ranges from 3-29%, while in Asia, it varies between 6.0-15.8%, and in Africa between 3.6-28.0%.[4,5]

Neonatal hyperbilirubinemia and kernicterus are frequently associated with G6PD deficiency, often without hematological evidence of hemolysis or identifiable triggers.[6] Research published by the American Academy of Pediatrics reported that G6PD-deficient and G6PD-intermediate infants experienced greater decreases in hematocrit, bilirubin levels, and need for phototherapy than G6PD-normal infants.[7]

Additionally, a study involving 100 neonates with moderate to severe indirect hyperbilirubinemia found that 16% were G6PD deficient, a substantial difference from the 6% control group. These neonates had higher serum bilirubin levels, requiring longer phototherapy and hospitalization. However, no significant differences were found in symptoms, reticulocyte counts, or age between G6PD-deficient and non-deficient groups, suggesting that hyperbilirubinemia severity in G6PD-deficient neonates is not solely due to excess hemolysis.[8]

A study involving 21,585 participants found that newborns with G6PD deficiency had a higher risk of hyperbilirubinemia with a pooled risk ratio of 3.92 and phototherapy with a pooled risk ratio of 3.01 in contrast to those with normal G6PD levels.[9] A study at Shaikh Zayed Hospital in Lahore, Pakistan, found that 6% of 100 neonates with hyperbilirubinemia were G6PD deficient, with higher bilirubin levels and lower platelet counts.[10] Glucose-6-phosphate dehydrogenase deficiency is prevalent in Al-Hasa, with a high incidence of 36.5% among all regions in Saudi Arabia.[2]

The present research study aimed to determine the incidence of hospitalized neonates with G6PD deficiency presenting with indirect hyperbilirubinemia at Almoosa Specialist Hospital, Al-Hasa, Saudi Arabia, over 4 years. Additionally, the study aimed to compare the therapeutic progression of G6PD-deficient and normal neonates admitted for indirect hyperbilirubinemia. The novelty of this research is in evaluating the significance of G6PD-normal and G6PD-deficient levels as quantitative indicators among hyperbilirubinemic males and females at Almoosa Specialist Hospital, Al-Hasa, Saudi Arabia.

Disclosure. Authors have no conflict of interests, and the work was not supported or funded by any drug company.

Methods. This retrospective case control study was carried out in the Neonatal Intensive Care Unit (NICU) at Almoosa Specialist Hospital in Al-Hasa, Saudi Arabia.

Almoosa Specialist Hospital is a specialized private tertiary hospital in the Eastern Province, equipped with 450 beds, including a Level 3 NICU with 30 beds, operating at an 80% occupancy rate. The hospital delivers approximately 3,500 neonates annually. The study comprised 2 groups with G6PD-deficient and G6PD-normal levels as outlined in Figure 1.

Data were collected retrospectively from 2018-2021 using the Yassasi Medical System, finalized in 2024.

Dependent variables analyzed included reason for admission, gestational age, birth weight, gender, onset of hyperbilirubinemia, total serum bilirubin (TSB) level, direct bilirubin level, hematocrit level, hemoglobin level, reticulocyte percentage, duration of phototherapy, and requirement for exchange transfusion. Independent variables included G6PD level (deficient or normal).

All neonates with a gestational age of less than 37 weeks and hyperbilirubinemia with additional risk

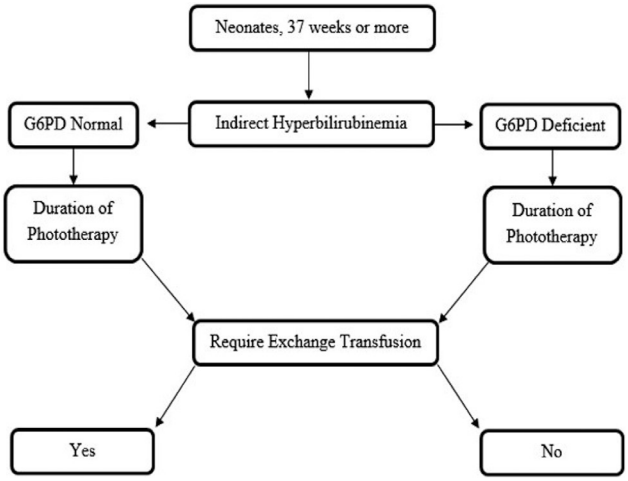

Figure 1 - Diagram illustrating the study design. G6PD: glucose-6-phosphate dehydrogenase

factors other than G6PD deficiency were excluded from the study. These risk factors included ABO incompatibility, Rh incompatibility, polycythemia, sepsis, and any condition known to contribute to hyperbilirubinemia, such as elliptocytosis, spherocytosis, and cephalohematoma. Neonates discharged against medical advice were also excluded to ensure accurate and comprehensive data analysis, particularly concerning the duration of phototherapy.

The study was carried out retrospectively using data collected from electronic databases without direct patient involvement. All collected data were securely stored in electronic systems protected by passwords and accessed only by authorized personnel. Patient identification remained confidential throughout the study. This research received a consent waiver from the institutional review board of Almoosa Specialist Hospital, Al-Hasa, Saudi Arabia, under log number: ARC-22-04-03.

Red blood cell G6PD activity was identified by quantifying the rate of increase in absorbance of nicotinamide adenine dinucleotide phosphate at 340 nm, expressed as units per gram of hemoglobin (U/gHb), following the method described by Beutler et al.[11] Measurements were carried out using a narrow-width (2 nm) spectrophotometer (Beckman model Du 60). A G6PD activity level below 3.36 U/gHb was considered deficient. Total serum bilirubin and conjugated bilirubin levels were determined using a modified diazo method on an automated clinical analyzer (Abbott, Alcyon 300).[12,13]

During hospitalization, the type of phototherapy (single, double, triple, or intensive) and the necessity for exchange transfusion were determined based on the TSB levels plotted on the hyperbilirubinemia nomogram used at Almoosa Specialist Hospital in Al-Hasa, Saudi Arabia, adapted from Fanaroff and Martin's neonatal-perinatal medicine.[14] Total serum bilirubin levels were monitored every 6-8 hours after phototherapy initiation to adjust the treatment intensity as indicated by the nomogram.

Following Kelsey's methods and considering a 95% confidence interval (CI) and a significance level (α, type 1 error rate) of 5%, a sample size of 268 was determined necessary to achieve 80% power (chance of detecting) for the study, assuming an odds ratio of 2. In this study, 3,200 neonates with hyperbilirubinemia were initially recruited, of which 2,926 did not meet inclusion criteria, primarily owing to incomplete G6PD level data. The final analysis focused on 274 hyperbilirubinemic neonates who fully met the inclusion criteria.

Statistical analysis. The Statistical Package for Social Sciences, version 19.0 (IBM Corp., Armonk, NY, USA) for Windows was used. Data were compared using mean, standard deviation, Student's t-test, Mann-Whitney-U test, and Chi-square tests. A p-value of <0.05 with a 95% CI was considered significant.

Results. Overall, our study included 274 neonates with indirect hyperbilirubinemia who met the inclusion criteria. Among them, 171 (62.4%) were G6PD-normal, comprising 82 (48%) males and 86 (52%) females. There were a total of 103 (37.6%) G6PD-deficient neonates, including 77 (74.8%) males and 26 (25.2%) females. Figure 2 summarizes the distribution of neonates included in the study.

Gender (males and females), gestational age, mode of delivery (normal vaginal delivery [NSVD] or caesarean section [CS]), Appearance, pulse, grimace, activity and respiration (Apgar) scores at 1 and 5 minutes, the onset of hyperbilirubinemia, highest total bilirubin level and its sampling time, direct bilirubin level, initial and lowest hemoglobin level and its sampling time, initial and lowest hematocrit level and its sampling time, percentage of reticulocytes and its sampling time, and duration of phototherapy were not statistically significant when comparing G6PD-normal and G6PD-deficient neonates with indirect hyperbilirubinemia, as presented in Table 1.

However, birth weight and weight upon admission were significantly higher in G6PD-deficient neonates compared to G6PD-normal hyperbilirubinemic neonates. Initial total bilirubin levels and sampling

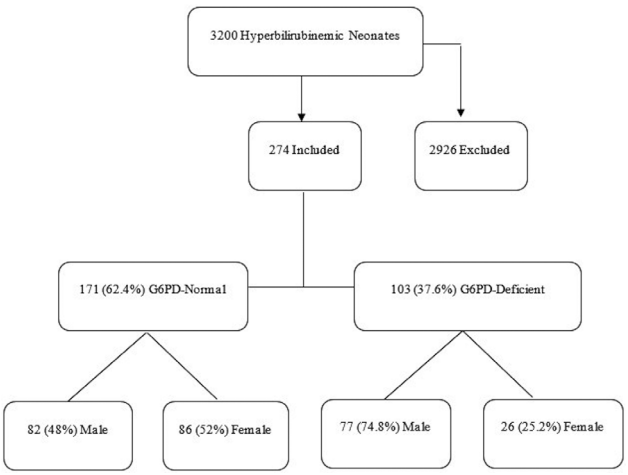

Figure 2 - The flowchart illustrating hyperbilirubinemic neonates included in the study categorized by glucose-6-phosphate dehydrogenase status. G6PD: glucose-6-phosphate dehydrogenase

Table 1 - Baseline and laboratory characteristics of hyperbilirubinemic neonates categorized by glucose-6-phosphate dehydrogenase deficiency status.

Characteristics	G6PD-normal	G6PD-deficient	*P*-values
Gestational age (weeks)	38.13±1.3	38.53±1.27	0.18
Birth weight (kg)	2.96±0.43	3.11±0.37	0.004
Weight upon admission (kg)	2.93±0.42	3.07±0.37	0.007
Gender, n (%)			
Male Female	82 (51.0) 89 (77.4)	77 (49.0) 26 (22.6)	≤0.0001
Mode of delivery, n (%)			
NSVD CS	122 (61.0) 49 (66.2)	87 (39.0) 25 (33.8)	0.484
Apgar score one minute	8.58±0.91	8.76±0.77	0.11
Apgar score 5 minuntes	9.77±0.7	9.88±0.42	0.128
Onset of hyperbilirubinemia (hour)	48±72	48±71	0.083
Initial total bilirubin level (µmol/L)	174.3±88.85	203.4±121	0.023
Initial total bilirubin level sampling time (hour)	48.15±43.9	61.12±52.66	0.029
Highest total bilirubin level (µmol/L)	229.34±88.14	253.02±129.8	0.74
Highest total bilirubin level sampling time (hour)	99.2±93.5	105.8±65	0.52
Direct bilirubin level (µmol/L)	9.81±10.7	9.80±6.3	0.995
Initial hemoglobin level (g/dL)	18.54±11.72	18.11±2.09	0.71
Initial hemoglobin level sampling time (hour)	4.87±19.4	9.66±33.6	0.136
Lowest hemoglobin level (g/dL)	15.41±3.23	14.98±3.63	0.451
Lowest hemoglobin level sampling time (hour)	116.95±140.8	126.45±141.2	0.7
Initial hematocrit level (%)	53.6±6.8	54.88±6.15	0.125
Initial hematocrit level sampling time (hour)	5.15±19.8	9.57±33.8	0.175
Lowest hematocrit level (%)	45.26±10.96	46.44±9.35	0.501
Lowest hematocrit level sampling time (hour)	127.54±154.7	114.8±117.9	0.591
Retics (%)	4.56±2.31	4.19±2.13	0.447
Retics sampling time (hour)	111.65±229.4	85.44±72.58	0.51
Duration of phototherapy (hour)	13.39±7.04	13.32±10.05	0.945
Requiring exchange transfusion, n (%)	0 (0.0)	4 (100)	0.009

Values are presented as numbers and percentages (%) or mean ± standard deviation (SD).
G6PD: glucose-6-phosphate dehydrogenase, NSVD: normal spontaneous vaginal delivery, CS: cesarean section

times were significantly higher in G6PD-deficient hyperbilirubinemic neonates. Out of the 274 neonates included in the study, only 4 required exchange transfusion as they were G6PD deficient, with a mean age of 90 hours, and this need was statistically significant with a *p*-value of 0.009 (2 [50%] G6PD-deficient males and 2 [50%] G6PD-deficient females).

The intensity of phototherapy, irrespective of gender and G6PD status, did not show statistical significance, as presented in Table 2.

When comparing hyperbilirubinemic males and females, there was no significant difference (p=0.793) in the initial total bilirubin level in G6PD-deficient males and G6PD-normal males and female patients (p=0.366). Similarly, there was no statistically significant difference (p=0.29) in the quantitative G6PD in G6PD deficient males compared to that of G6PD deficient females. However, G6PD-normal females had significantly lower G6PD levels compared to G6PD-normal males, as depicted in Table 3.

Regarding blood groups and their association with G6PD status, blood group O positive was the most prevalent among both G6PD-normal and G6PD-deficient individuals, as depicted in Figure 3. However, this relationship was not statistically significant (p=0.884).

Discussion. The initial total bilirubin level in G6PD-deficient hyperbilirubinemic neonates was significantly higher than in G6PD-normal hyperbilirubinemic neonates, consistent with previous findings.[10,15,16] Neonatal hyperbilirubinemia is frequently associated with G6PD deficiency and, in many cases, occurs without hematological evidence

Table 2 - The intensity of phototherapy in hyperbilirubinemic neonates categorized by glucose-6-phosphate dehydrogenase deficiency status.

Intensity of phototherapy*	G6PD-normal	G6PD-deficient	Total
Single	27 (65.5)	13 (32.5)	40 (14.6)
Double	62 (64.6)	34 (35.4)	96 (35.0)
Triple	56 (62.9)	33 (37.1)	89 (32.5)
Intensive	26 (53.1)	23 (46.9)	49 (17.9)

Values are presented as numbers and percentages (%). *Statistically not significant with a *p*-value of <0.05. G6PD: glucose-6-phosphate dehydrogenase

Table 3 - Laboratory characteristics and intensity of phototherapy in hyperbilirubinemic neonates with glucose-6-phosphate dehydrogenase deficiency and normal levels, categorized by gender.

G6PD status	Male	Female	*P*-values
Initial total bilirubin level (µmol/L), mean±SD			
Deficient	205.29±124.58	198.04±111.95	0.793
Normal	180.7±76.83	168.35±98.8	0.366
G6PD level (U/gHb), mean±SD			
Deficient	0.89±1.98	1.41±2.66	0.29
Normal	10.57±4.01	8.6±4.81	0.004
Intensity of phototherapy (G6PD-normal)*			
Single	16 (19.5)	11 (12.4)	
Double	27 (35.9)	35 (39.3)	
Triple	27 (35.9)	29 (32.6)	
Intensive	12 (14.6)	14 (15.7)	
Intensity of phototherapy (G6PD-deficient)*			
Single	8 (10.4)	5 (19.2)	
Double	27 (35.1)	7 (26.9)	
Triple	23 (29.9)	10 (38.5)	
Intensive	19 (24.7)	4 (15.5)	

Values are presented as numbers and percentages (%) or mean±standard deviation (SD). *Statistically not significant with a *p*-value of <0.05. G6PD: glucose-6-phosphate dehydrogenase

of hemolysis or an identifiable trigger, as our findings suggest, with an insignificant relation to reticulocyte levels.[17,18] The significance of the sampling time of initial total bilirubin in G6PD-deficient neonates, with a mean age of 61 hours, aligns with the American Academy of Pediatrics' publication of a study carried out in Nigeria. This study suggests that G6PD-deficient neonates require greater monitoring and early screening in the first week of life, even in the absence of exposure to icterogenic agents.[19]

The onset of hyperbilirubinemia, highest bilirubin level, and duration of phototherapy were not significantly related to G6PD status in previous studies or our study.[15,20] Our study also included the intensity of phototherapy categorized as single, double, triple, or intensive which was not statistically significant ($p<0.05$). This study included males and females and found no significant relationship between G6PD deficiency and hematocrit or hemoglobin levels. This contrasts with a study by Al-Abdi et al[21] in males from the Al-Hasa region, which concluded that G6PD-deficient individuals had higher hematocrit and hemoglobin levels.

Another study concluded that G6PD-deficient individuals had lower hematocrit levels.[22,23] Previous studies have found a high incidence of exchange transfusions among G6PD-deficient neonates, including a study of Sephardic-Jewish infants where only 2 out of 75 G6PD-deficient neonates required such treatment compared to none among 266 with normal G6PD status.[24,25] In our study of 274 neonates, only 4 required exchange transfusion, with a mean age of 90 hours, which was statistically significant ($p=0.009$) in the G6PD-deficient group: 2 (50%) G6PD-deficient males and 2 (50%) G6PD-deficient females.

While G6PD deficiency is predominantly observed in males, a study carried out in Turkey found that among 46 G6PD-deficient neonates, only 12 (26%) were females, a ratio similar to our findings where 26 (25.2%) out of 103 G6PD-deficient neonates were females, highlighting the importance of including

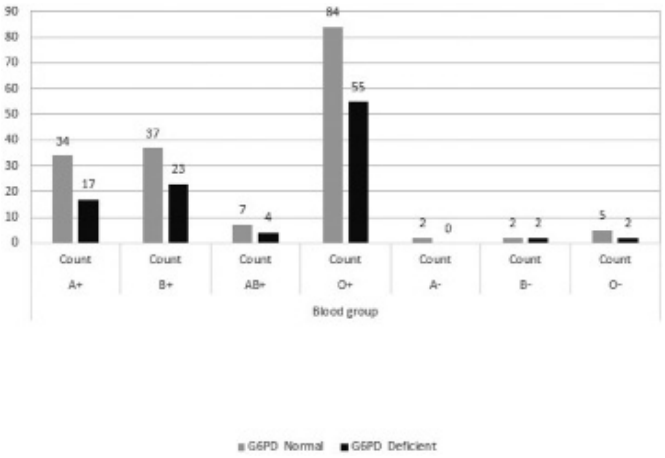

Figure 3 - Hyperbilirubinemic neonates with glucose-6-phosphate dehydrogenase deficiency and normal levels, categorized by blood group. G6PD: glucose-6-phosphate dehydrogenase

females in G6PD screening.[24] Our study quantitatively assessed G6PD levels, revealing a significant finding: G6PD-normal hyperbilirubinemic females had lower G6PD levels compared to G6PD-normal hyperbilirubinemic males, which was statistically significant ((p=0.004). However, this difference was not significant in the G6PD-deficient group despite lower levels in G6PD-deficient males. Birth weight and weight at admission were significantly higher in G6PD-deficient neonates, suggesting that hyperbilirubinemia in G6PD-normal neonates was often associated with breastfeeding jaundice, especially in early life. Inadequate breastfeeding leads to insufficient caloric intake and dehydration. Insufficient feeding reduces bowel movements, reducing bilirubin elimination through the stool, resulting in an accumulation of unconjugated bilirubin in the bloodstream. Furthermore, these findings indicate that G6PD deficiency alone could account for hyperbilirubinemia without triggering hemolysis. Blood group O positive was the most common blood type associated with G6PD deficiency, consistent with our findings.[21] However, ABO blood type did not show a significant association with hyperbilirubinemia in G6PD-normal and deficient neonates.

Study limitations. It is important to note that our study was retrospective and confined to a single private tertiary centre in Al-Hasa, Saudi Arabia. It did not include neonates with indirect hyperbilirubinemia who might have been readmitted or followed up at other hospitals. Therefore, further research encompassing multiple regions is needed to elucidate the exact relationship and underlying mechanisms of G6PD deficiency in neonates with hyperbilirubinemia.

In conclusion, G6PD deficiency screening should be strongly considered, especially in regions with high prevalence, such as Al-Hasa, Saudi Arabia. As depicted in the present study, G6PD-deficient neonates require more vigilant monitoring for hyperbilirubinemia to enable early detection in the first week of life, ideally by 90 hours of age. This recommendation is supported by specific findings from our study. Firstly, G6PD-deficient neonates exhibited significantly higher initial total bilirubin levels compared to G6PD-normal neonates (203.4±121 µmol/L vs. 174.3±88.85 µmol/L, p=0.023). Additionally, all neonates who required exchange transfusion due to severe hyperbilirubinemia were G6PD-deficient, a finding that was statistically significant (p=0.009). Specifically, out of the 274 neonates included in the study, the 4 who needed exchange transfusion were all G6PD-deficient, with a mean age of 90 hours at the time of the procedure. These results indicate that G6PD-deficient neonates are at a higher risk of developing severe hyperbilirubinemia that may necessitate more intensive treatment, such as exchange transfusion.

Acknowledgment. *The authors gratefully acknowledge Falcon Scientific Editing for their English language editing.*

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