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Prevalence and Mothers' Perception of Glucose-6-Phosphate Dehydrogenase Deficiency among Egyptian Jaundiced Neonates

Running title: G6PD deficiency among Jaundiced Neonates

Zeinab A. Kasemy[1], Safa H. Al Kalash[2], Wael A. Bahbah[3] Sally M. El Hefnawy[4]

1Public health and community medicine department, Menoufia faculty of medicine, Egypt

2Family medicine department, Menoufia faculty of medicine, Egypt

3Pediatrics department, Menoufia faculty of medicine, Egypt

4Biochemistery department, Menoufia faculty of medicine, Egypt

Corresponding author:

Zeinab Abdel Aziz Kasemy

Tel: +201068787807

Address: Gamal Abdel Nasser st, 5th floor, public health department, Faculty of medicine, Shibin ELkom, Menoufia, Egypt

E.mail: zeinabkasemy@yahoo.com , zeinabkasemy@gmail.com , zeinab.kasemy@med.menofia.edu.eg

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Abstract:

Objectives: To estimate the prevalence of Glucose 6 phosphate dehydrogenase (G6PD) deficiency among Egyptian jaundiced neonates and assessing the mothers' perception towards G6PD and Neonatal jaundice (NNJ).

Background: NNJ is a frequent complication of G6PD deficiency.

Methods: A cross-sectional study was carried out on 487 Egyptian neonates with indirect hyperbilirubinemia from June 2018 to July 2019. The collected data included maternal and neonatal characteristics. Laboratory investigations included serum bilirubin, reticulocyte count, ABO grouping, Rh typing, and neonatal serum G6PD. The mothers were interviewed individually using a structured, researcher administered questionnaire for assessing the perceptions of G6PD deficiency and NNJ.

Results: Prevalence of G6PD deficiency had been reported in 10.10%. Regarding bilirubin level, neonates with G6PD deficiency showed higher levels of serum bilirubin (P<0.001). Male sex, positive family history, and positive consanguinity worked as risk factors for G6PD deficiency (OR=4.27, 9.54 and10.21 respectively). Regarding mothers' perception towards NNJ and G6PD, it was low towards both diseases, where good knowledge was reported in 30% for NNJ vs. 17.10% for G6PD deficiency, positive attitude (46.8% for NNJ vs. 45.0% for G6PD deficiency) and finally good practice (29.9% for NNJ vs. 19.9% for G6PD deficiency)

Conclusion: G6PD deficiency seems to be an important cause of NNJ. The study revealed that mothers' perception of NNJ and G6PD deficiency was low. A mass health education program about G6PD deficiency and NNJ is needed to ensure better early detection, good timing treatment and better prevention of the triggering factors to ensure better health of the children.

Keywords: Awareness, G6PD deficiency, NNJ, Perception, KAP, Child health, Eidemiology

Strength and limitations:

Strengths:

- The study collectively assessed the prevalence and risk factors of G6PD deficiency besides assessing the level of knowledge, attitude, and practice (KAP) regarding both of G6PD deficiency and neonatal jaundice (NNJ) in our environment.
- The study clarified the extent of change towards NNJ based on previous levels published in some research articles in the same region and also drew how much G6PD deficiency despite being a serious disease; it is a poorly known one, making a special recommendation of health education sessions for every mother to be conducted in health centers from day one.
- A suitable sample size had been studied in a short period, which allowed us to reach large number of mothers and families.

Limitations:

- We reached only the mothers who sought medical advice for their neonates. Both diseases need KAP assessment among the general population to ensure taking care of the risk factors, but we tried to help the mothers be messengers to their families specially after conducting a health education session during the day organized to thank them for participation in the study.
- Unfortunately, there was a need to perform a posttest to assess the extent of understanding and KAP among the studied mothers to ensure providing right message, but it was difficult to collect this studied number one more time

Introduction:

The term 'jaundice' is used to describe the yellow-orange discoloration of the skin and sclera because of excessive bilirubin in the skin and mucous membranes. (1) It is not a disease, but rather a symptom or sign of a disease. (2) Jaundice (Hyperbilirubinemia) though a common benign occurrence in the 1st week of life can sometimes progress to critical levels. (3) Neonatal jaundice is a frequent complication of Glucose 6 phosphate dehydrogenase (G6PD) deficiency which is a genetic disease frequently affects males. (4, 5) African, Asia, Mediterranean, and Middle-Eastern descents are most commonly affected by this disorder (6, 7) Prevalence of G6PD

deficiency among Egyptian neonates is (8.9%). (8) The disease was reported for the first time in India, and then it reaches in some countries up to 25% prevalence. (9) The commonly asymptomatic G6PD deficiency can be triggered by some agents like specific foods, drugs, and infections which may result in a hemolytic reaction. (5) Treatment for G6PD deficiency is simple and inexpensive (9) and can be started before symptoms appear. (10, 7) Counseling should be directed to parents of deficient newborns to avoid risks of jaundice and triggering agents. (9). Studying the level of knowledge, attitude, and practice about G6PD and neonatal jaundice in our environment, to allow ensuring the avoidance of triggering factors is essential. So this study aimed to estimate the prevalence of G6PD deficiency among Egyptian jaundiced neonates and assessing the mothers' perception through studying their level of knowledge, attitude and practice regarding G6PD and neonatal jaundice.

Subjects & Methods:

A cross-sectional study was carried out in Egypt on 487 neonates with indirect hyperbilirubinemia in time frame of 12 months (from June 2018 to June 2019). The study had been approved by the local ethical committee and after explanation of the study, written consent had been received from parents and caregivers. Up to 10 days of age with clinically evident jaundice, admitted term and preterm neonates were included in the study. The exclusion criteria included neonates with direct hyper-bilirubinemia (> 20%), metabolism errors, congenital anomalies and sepsis. The collected data included maternal and neonatal characteristics in the form of gestational age, parity, gravidity, neonatal sex, weight, and jaundice age of onset. The studied neonates had been subjected to laboratory investigations including serum bilirubin (total, direct, indirect), reticulocyte count, ABO grouping and Rh typing of the mother and baby, Coombs test and C reactive protein. UV-Kinetic Method using cellular enzyme determination reagents by spectrophotometry was used to measure quantitative estimation of serum G6PD by using 1ml of whole blood collected in an EDTA tube. Level <4.6 u/g Hb was estimated to define G6PD deficiency. For assessing the perceptions of G6PD deficiency and neonatal jaundice, the mothers were interviewed individually using a researcher administered questionnaire about their idea about neonatal jaundice (NNJ) and G6PD. For NNJ, the questionnaire included questions like mother's knowledge regarding its diagnosis, causes, complications and treatment.

Regarding the attitude of mothers toward NNJ and its treatment; the questions included if the mother thinks that NNJ is a worrisome condition, etc. For practice, if she would seek medical advice. Etc. Regarding G6PD deficiency, the questionnaire included questions like if G6PD; is a Blood disease, both parents have to be carriers for G6PD, the inheritance of G6PD related to the baby's gender, agents that can trigger an attack of G6PD like Fava beans and medications, is pallor, giddiness, shortness of breath or jaundice a symptom of G6PD attack, are GIT symptoms like (nausea and vomiting) are symptoms of G6PD attack. Regarding attitude, if she sees that this is a serious problem, marriage between contagious couples is a cause, etc. Regarding practice, the questionnaire included; seeking medical advice, premarital counseling, etc.., With answers scored as correct = 1 and incorrect = 0; participants with at least 60% correct answers were considered as having good knowledge. Participants with at least 60% positive answers were considered as having a positive attitude and practice. A health education talk was given by the researcher to the participant mothers, with adequate clarification.

Sample size calculation: Based on past review of literature (8) who reported that prevalence of G6PD among jaundiced newborn to be 8.9%, sample size has been calculated using the following equation: $n = (z^2 \times p \times q)/ D2$ at CI 95% and it was estimated to be 487 jaundiced neonates

Statistical analysis: Data were analyzed by using SPSS version 22 (SPSS Inc., Chicago, IL, USA). An independent t-test and ANOVA test were used for normally distributed quantitative. Chi-square ($\chi 2$) was used for qualitative variables. Odds ratio (OR) was used to assess the risk of exposure. P-value less than 0.05 was considered statistically significant.

Patient and Public Involvement:

This work aimed to study the prevalence of G6PD deficiency among Egyptian jaundiced neonates and mothers' perception regarding both diseases. To improve the relevance of research, oriented research including patient and public is vital. A paper-based survey asked some mothers seeking medical advice in some neonatal and pediatric centers to submit their unanswered questions regarding G6PD and NNJ. The final top four research priorities in an in-person meeting were ranked. Thirty respondents submitted forty questions. The respondents were from urban and rural areas. Their ages ranged from 20-40 years. The forty questions were distilled to

seventeen unique questions and from this list; the top four research questions prioritized included if these diseases are infectious ones, if they can be transferred to the next generations, if they are long-life diseases and if there is a complete cure. The respondents were subjected to questionnaires by observers to assess the degree of response and reactivity. The interviewed mothers recommended to generalize the screening over large number and to be in the most crowded districts, so we asked them to tell every pregnant woman they know to seek medical advice for free in certain neonatal centers, where we are working, if there is a doubt of having a yellow baby to encourage them participate in the study. We organized a special day in our region in order to thank all participants in the first place, disseminate the results and provide in-depth health education session about the two diseases. The main aim of the health education session was to correct the wrong information and to build a base for new mothers' generation who know well these diseases and be messengers to their families and surroundings.

Results:

The study was conducted on 478 Egyptian jaundiced neonates. The mothers' age ranged from 22-39 years (31.45 ±4.77). Neonates aged (0-10 days) were distributed in 69.6% males versus 30.4% females. Their birth weight ranged from (2.30-3.50 Kg). Bilirubin levels were distributed into total (15.17 ±5.14), Direct (1.08 ±0.38) and indirect (13.17 ±3.74). Mean Hb showed a good level of about (12.18 ±1.75) despite low and high range (9.50-14.50). **(Table 1)** Prevalence of G6PD deficiency had been reported in 10.10% (<4.6 u/g Hb). **(Fig 1)** Regarding bilirubin level, neonates with G6PD deficiency showed higher levels of bilirubin (total, direct and indirect) (P<0.001). Male sex showed that it is riskier to G6PD deficiency (OR=4.27, CI95%: **1.66-10.99**). Also, neonates with a positive family history of G6PD deficiency and a positive consanguinity seemed to be more at risk of acquiring G6PD deficiency (OR=9.54, CI 95% 4.80-18.95) and (OR=10.21, CI 95%: 5.39-19.33) respectively. **(Table 2)** Positive correlation had been noticed between G6PD and jaundice time of onset**. (Fig 2)** One of the interesting findings was that total bilirubin was higher in G6PD deficient cases (23.03 ±2.94) than those with RH (15.7 ±4.75) or ABO incompatibility (11.0 ±2.59) **(Fig. 3).** Regarding knowledge, attitude and practice (KAP) towards NNJ and G6PD, it seems that mothers showed somehow better perception towards jaundice in comparison to G6PD deficiency, but unfortunately KAP was low towards both diseases as majority of mothers (95.9%) didn't know term (G6PD deficiency) while about 24% of them heard about fava bean anemia, also 90%of them didn't know that both parents

have to be carriers for G6PD deficiency to have an affected child. All mothers knew about fava beans can trigger an attack of G6PD deficiency while 39.3% knew that it is triggered by drugs **(Table 3).** Almost all mothers know about neonatal jaundice, about 70% of them thought that prematurity is a cause of neonatal jaundice, 68.6% of the mothers knew that they can detect jaundice in their newborn in skin while 25% of them reported that jaundice can be defined in sclera of newborn about 95% of the mothers knew that phototherapy is method of treatment of NJJ**.(Table 4)** Good knowledge was reported in 30% for NNJ vs. 17.10% for G6PD deficiency, positive attitude was reported in 46.8% for NNJ vs. 45.0% for G6PD deficiency and finally good practice was reported in 29.9% for NNJ vs. 19.9% for G6PD deficiency **(Fig. 4)**

Discussion:

Worldwide, G6PD deficiency is the most commonly deficient enzyme. African, Asia, Mediterranean, and Middle-Eastern descents are most commonly affected by this disorder. In the current study; the prevalence of G6PD deficiency had been reported in 10.1% of jaundiced neonates which lied in the range of 8.9-30.2% of the prevalence of G6PD deficiency in Egyptian studies conducted in Egyptian governorates, Menoufia and Giza, which revealed that G6PD deficiency represented 8.9 % and 30.2% respectively among jaundiced newborns. (8, 11) The higher prevalence of G6PD deficiency among jaundiced neonates in El-Menshay et al., (11) may be due to nature of the chosen small sized purposive sample. This wide range could be explained by that special Egypt's geographical position between three continents with different ethnic groups results in wide variation of the prevalence of G6PD deficiency in different sectors, which is the same case on global scale where in Iraq, prevalence was 10.65% (12), in Iran, it was around 9% (13) and in South Brazil it was 7.9%. (14) Regarding bilirubin level in the present study, neonates with decreased G6PD showed higher levels of bilirubin and this result goes parallel to that of Bahraini and Nigerian studies conducted by Isa et al., (15) and Badejoko et al., (16) respectively. Male sex showed to be more risky to G6PD deficiency which is similar to findings reported in Egypt by Abo El Fotoh and Rizk (8), Abo Elella et al., (10) and El-Menshay et al.,(11), in India by Sinha et al., (17) and in Iran by Eghbalian and Monsef (18). In the current study; neonates with a positive family history of G6PD deficiency and a positive consanguinity were more at risk of acquiring G6PD deficiency which is in line with an Egyptian study conducted by Abo El Fotoh and Rizk (8). In India, Garg and Joag (19) found that about 20.4% of neonates with G6PD deficiency born from consanguineous parents. On the contrary a study

conducted in Japan concluded that only one case of G6PD deficiency was detected and born to non-consanguineous, Japanese parents without any family history. (20) The current study found a positive correlation between G6PD deficiency and jaundice time of onset. As known, two peaks for jaundiced patients to be admitted, the first is on the 3rd day and the second is on the 7th day of life. Bimodal peaks of maximum serum bilirubin concentrations are known to happen among G6PD deficient infants and when the hemolytic episode starts early, the elevation of serum bilirubin is anticipated to be clear and hence a course of hyperbilirubinemia may, therefore, be predicted. (21) The finding is in agreement with Abo El Fotoh and Rizk (8). But it is in disagreement with result of Turkish study conducted by Atay et al., (22) who reported a non-statistical difference was detected between G6PD-deficient and normal groups concerning the time of onset of jaundice. Regarding total bilirubin level; the present study reported that it was obviously higher in G6PD deficient cases than those with RH or ABO incompatibility and this finding agrees with that concluded by Das and Singh (23) in India and Hussain et al., (24) in Pakistan who found that serum bilirubin level was higher among G6PD deficient neonates than those suffered from RH and ABO incompatibility. In contrary to this finding, the results obtained by Shah and Yeo (25) in Singapore and Aletayeb et al.(26) in Iran who showed no significant difference in serum bilirubin level in G6PD deficiency, ABO or RH incompatibility. Regarding knowledge, attitude and practice towards jaundice and G6PD, majority of mothers (95.9%) didn't know the term (G6PD deficiency) which isn't agreed with Al-Joborae, (27) who found that about 91% of mothers in Iraq heard about G6PD deficiency. In Egypt, the most commonly used term is “Fava bean anemia”, so in our study, 23% of mother heard about Fava bean anemia but 4.1% only knew the term “G6PD deficiency anemia”. All mothers knew that fava beans can trigger an attack of G6PD deficiency, hence the term came from, which is in agreement with a study carried out in Bahrain by Al Arrayed and Al Hajeri, (28). In our study, about 40% of mother thought that hemolysis can be triggered by some sort of drugs and this result is inconsistent with that obtained by Almuhaini et al., (29). Regarding mother's knowledge about neonatal jaundice, all mothers heard about it and about 40% of them reported that prematurity of the infant is a cause of its occurrence and this result is consistent with that provided by Magfouri et a., (30) in Saudi Arabia as they found that 54.5% of the respondent said that prematurity of newborn is a cause for NNJ. Also in the present study, 68.6% of the mothers knew that they can detect jaundice in their newborn in the skin while 25% of them reported that jaundice can be defined in

the sclera of a newborn. These findings agree with that achieved by Aggarwal et al., (31) in India who reported that 50.6% of the mothers can identify the correct site to detect jaundice in newborns. It seems that mothers showed somehow better perception towards jaundice in comparison to G6PD deficiency. This is in agreement results reported by Boo et al., (32) in Malaysia. Our results still showed poor KAP regarding both diseases. This is in agreement with Goodman et al., (33) in Nigeria who found that most of the mothers had poor knowledge about neonatal jaundice, Alfouwais et al., (34) in Saudi Arabia who revealed that knowledge of Saudi parents about neonatal jaundice was average. The study results showed some improvement in level of knowledge in comparison with Allahaony et al (35) who reported regarding NNJ that only 18.9% of mothers had good knowledge, 48.0% had good attitude and only 25.3% had a good practice, which shows the effect of health education carried out to the mothers but it shows also that we are still in a bad need to more extensive and focused health education. (Sadat et al., (36) and Rabiyeepoor, (37) in Iran reported that risk factors for hyperbilirubinemia were ABO incompatibility, prematurity, and infection. In contrast to the study results, Al-Joborae, (27) in Iraq and Al Arrayed et al., (28) reported that the mothers had a fairly good level of awareness of G6PD deficiency.

Conclusion: G6PD deficiency seems to be an important cause of neonatal jaundice. Cord blood G6PD screening is better to be performed in high-risk populations, to early consider a prolonged hospital stay after birth. G6PD deficiency and NNJ are serious conditions so be studying KAP of mothers about them, the study revealed that mothers' KAP about neonatal jaundice despite being still low but it shows promising improvement while KAP about G6PD deficiency is so poor. So it so evitable to apply a mass health education program about G6PD deficiency and also NNJ to ensure better early detection, good timing treatment and better prevention of the triggering factors to ensure better health of the children.

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Ethical Approval: Institutional Review Boards (IRB) of the Menoufia faculty of medicine had approved the study. Research work had been performed in accordance with the Declaration of Helsinki. A written patient's Consent was taken after explanation of all aspects of the study and gave them the right to withdraw at any time.

Data sharing statement: Data are available to be shared on request by e. mailing zeinabkasemy@yahoo.com

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Legend of figure:

Fig 1: Prevalence of G6PD deficiency among the studied jaundiced neonate group

Fig 2: Correlation between G6PD and Jaundice time of onset in deficient cases

Fig 3: Total bilirubin distribution among patients with G6PD deficiency, RH incompatibility and ABO incompatibility

Fig 4: Perception of G6PD deficiency and neonatal jaundice among the studied mothers

Table 1: General characteristics of the studied mothers and jaundiced neonates :

General characteristics	Study group (n=487)	
	Mean ±SD	Range
Mothers' characteristics		
Age (Y)	31.45±4.77	22-39
Gestational age(week)	37.71±1.05	37-41
BMI(kg/m2)	22.02 ±2.37	18.30-27.10
	no	%
Gravidity		
≤3	292	60.0
>3	195	40.0
Parity		
≤2	252	51.7
>2	235	48.3
Neonatal characteristics	Mean ±SD	Range
Sex: no,%		
Mae	339	69.6
Female	148	30.4
Birth weight (kg)	2.60±0.29	2.30-3.50
Bilirubin		
• Total	15.17 ±5.14	7.30-25.50
• Direct	1.08±0.38	1.50-0.50
• Indirect	13.17 ±3.74	6.40-23.15
Hb (gm/dl)	12.18 ±1.75	9.50-14.50
Reticulocyte count (%)	3.38 ±1.30	1.40-6.0

Table 2: Distribution of the studied G6PD groups regarding bilirubin, neonate sex, family history and consanguinity:

	G6PD						
	Deficient No.=49		Normal No. =438		Test of sig	P value	OR CI 95%
	no	%	no	%			
Bilirubin (mean ±SD)							
• **Total**	23.0 3±2.94		14.30 ±4.55		**t=18.40**	**<0.001***	-
• **Direct**	1.38 ±0.14		1.02 ±0.41		**t=12.47**	**<0.001***	
• **Indirect**	17.02 ±3.45		12.74 ±3.52		**t=8.21**	**<0.001**	
Neonate Sex							
Male	42	85.7	297	45.0	**χ^2=10.49**	**0.001***	**4.27(1.66-10.99)**
Female	7	14.3	141	55.0			**1.0**
Family history of G6PD							
+ve	37	75.5	107	24.4	**χ^2=55.21**	**<0.001***	**9.54(4.80-18.95)**
-ve	12	24.5	331	75.6			**1.0**
Consanguinity							
+ve	33	67.3	70	16.0	**χ^2=69.72**	**<0.001***	**10.21(5.39-19.33)**
-ve	16	32.7	368	84.0			**1.0**

***Significant**

Table 3: Knowledge, attitude and practice of the studied mothers regarding G6PD deficiency:

Knowledge	No.=487 no	%
Hearing about G6PD deficiency		
- Yes	2	4.1
- No	485	95.9
Hearing about fava bean anemia		
• Yes	112	23.0
• No	375	76.0
G6PD is a blood disease		
- Yes	100	89.3
- No	12	10.7
- I don't know	0	0.0
Is it a hereditary disease:		
• Yes	105	93.8
• No	5	4.5
• I don't know	2	1.8
Both parents have to be carriers for G6PD deficiency to have an affected child?		
- Yes	5	4.5
- No	1	0.9
- I don't know	101	90.2
The inheritance of G6PD deficiency related to the baby's gender?		
- Yes	10	8.9
- No	3	2.7
- I don't know	99	88.4
Knowing whether personally you may have a G6PD deficiency child		
- Yes	8	7.1
- No	85	75.9
- I don't know	29	25.9
There should be a family history of G6PD deficiency to result		
- Yes	75	67.0
- No	15	13.4
- I don't know	62	55.4
Fava beans can trigger an attack of G6PD deficiency		
- Yes	112	100.0
- No	0	0.0
- I don't know	0	0.0
Some medications Can trigger an attack of G6PD deficiency		
• Yes	44	39.3
• No	10	8.9
• I don't know	58	51.8
Symptoms of G6PD attack:		
Pallor		
• Yes	10	8.9
• No	52	46.4
• I don't know	60	53.8
Nausea, vomiting, anorexia and diarrhea		
• Yes	15	13.4
• No	45	40.2
• I don't know	52	46.4
Giddiness		
• Yes	30	26.8
• No	5	4.5
• I don't know	77	68.8
Jaundice		
• Yes	105	93.8
• No	2	1.8
• I don't know	5	4.5
Shortness of breath		
• Yes	35	31.3
• No	5	4.5
	72	66.1
Attitude	**no**	**%**
Is this a serious problem		
- Yes	100	89.3
- No	5	4.5
- I don't know	7	6.3
Consanguinity is the cause of the disease		
- Yes	40	35.7
- No	20	17.9
I don't know	52	4.3
Next pregnancy should be prevented:		
- Yes	3	2.7
- No	50	44.6
- I don't know	59	52.7
Follow-up of the diseased child should continue for life	100	89.3
- Yes	2	1.8
- No	10	8.9
- I don't know		
Practice	**no**	**%**
Have you been subjected to premarital counseling	112	100.0
- Yes	0	0.0
- No		
Have you been subjected to genetic screening		
- Yes	2	1.8
- No	110	98.2
- I don't know	0	0.0
Seeking medical advice after delivery to be assured	0	0.0
- Yes	112	100.0
- No		

Table 4: Knowledge, attitude and practice of the studied mothers regarding NNJ:

Knowledge	No.=487 no	%
Hearing of NNJ		
Yes	487	100.0
No	0	0.0
Site to detect NNJ		
Skin	334	68.6
Eye	123	25.2
Tongue	30	6.2
Causes		
Prematurity	341	70.0
ABO disparity between mother and baby	73	15.0
Breastfeeding	146	30.0
Infection	139	33.0
Hemolysis	194	39.8
Dehydration	170	34.9
Increased U/S examination during pregnancy	292	60.0
Diabetic mothers	73	15.0
Others	141	28.9
Complications		
Death	146	30.0
Cerebral palsy	112	23.0
Mental retardation	170	34.9
Handicapping	112	23.0
Hearing loss	30	6.2
Methods of treatment		
Phototherapy	461	94.7
Blood exchange transfusion	146	30.0
Drugs	399	82.0
Neon lamp	364	74.7
Increase breastfeeding	238	48.9

Attitude	no	%
NNJ is a worrisome condition?		
- Yes	248	50.9
- No	200	41.1
- I don't know	39	8.0
Phototherapy is the best way in treatment		
- Yes	409	84
- No	8	1.6
- I don't know	70	14.4
Blood exchange transfusion is the best way of management	107	22
- Yes	50	10.3
- No	330	67.7
- I don't know		
Is it important seeking medical advice		
- Yes	450	92.4
- No	20	4.1
- I don't know	18	13.5

Practice	no	%
Seeking a medical advice if having baby with NNJ		
- Yes	477	95.9
- No	10	4.1
- I don't know	0	0.0
Causes of denial of medical care :	N=10	
- Afraid of hospitalization.	6	60.0
- Admission/ investigation not required.	**1**	10.0
- High cost of medical care.	2	20.0
- Lack of transportation.	0	0.0
- Long hours to reach hospital**.**	0	0.0
Time of seeking medical advice within 24 h		
- 24-48 h	136	28.5
- ≥ 3 days	341	71.5
Continuation of breastfeeding		
- Yes	448	92.0
- No	39	8.0

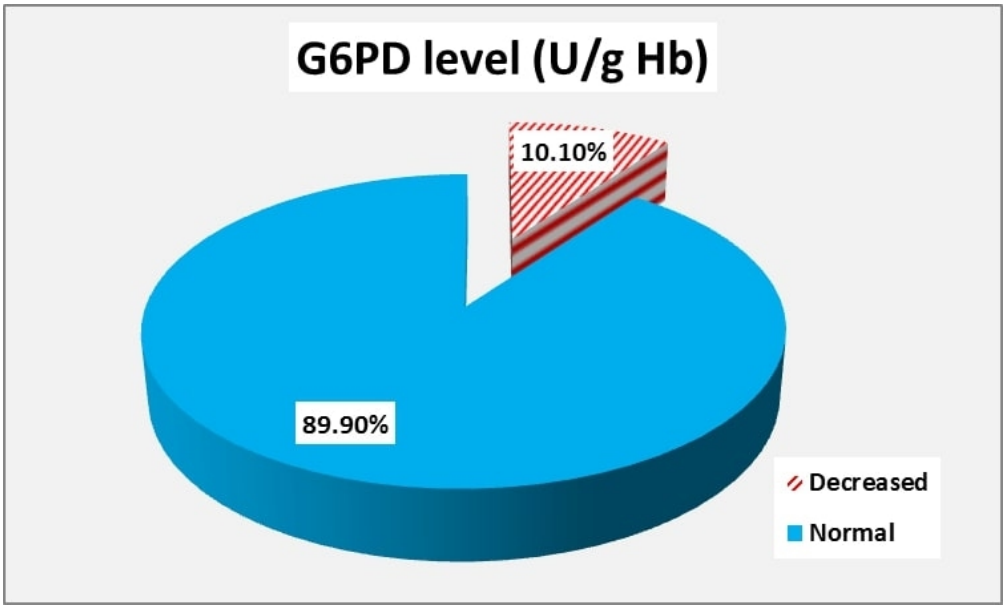

Fig 1: Prevalence of G6PD deficiency among the studied jaundiced neonate group

265x159mm (72 x 72 DPI)

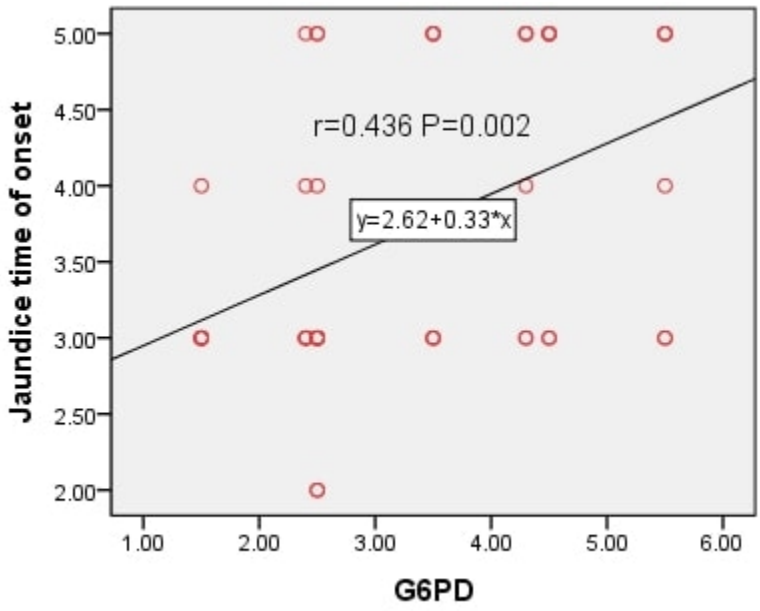

Fig 2: Correlation between G6PD and Jaundice time of onset in deficient cases

138x110mm (72 x 72 DPI)

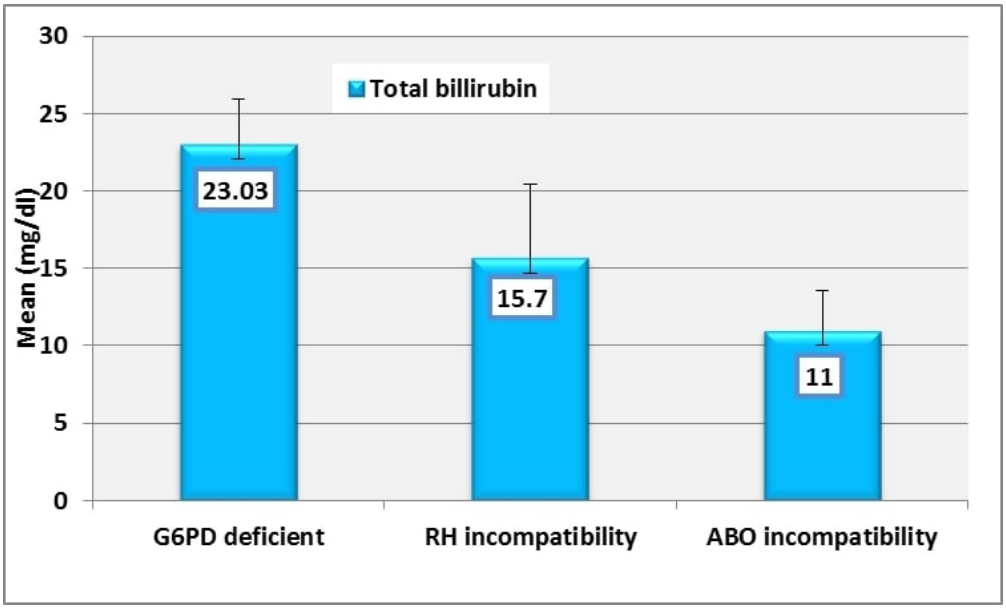

Fig 3: Total bilirubin distribution among patients with G6PD deficiency, RH incompatibility and ABO incompatibility

265x159mm (72 x 72 DPI)

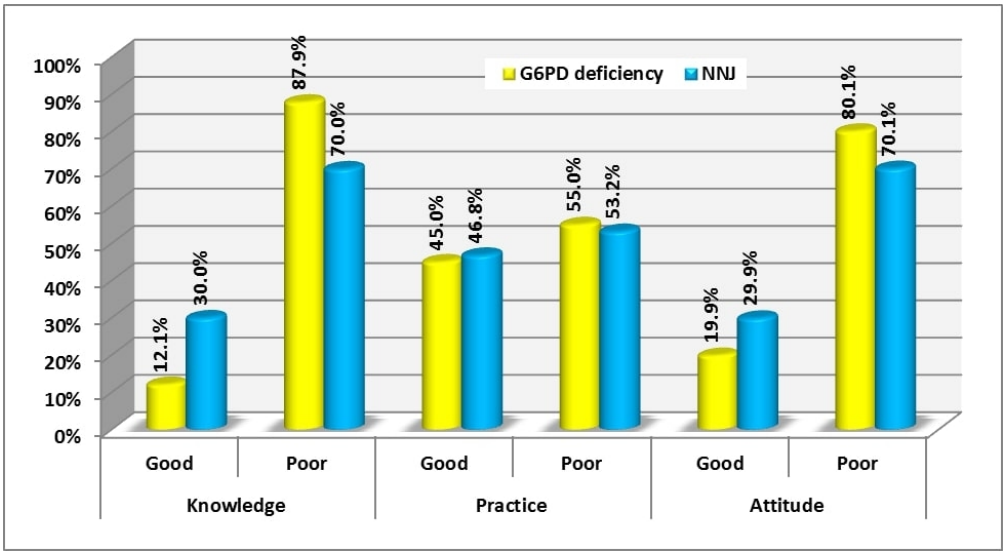

Fig 4: Perception of G6PD deficiency and neonatal jaundice among the studied mothers

343x188mm (72 x 72 DPI)

BMJ Open

Prevalence and Mothers' Knowledge, Attitude and practice of Glucose-6-Phosphate Dehydrogenase Deficiency among Jaundiced Neonates: A cross-sectional study

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Prevalence and Mothers' Knowledge, Attitude and practice of Glucose-6-Phosphate Dehydrogenase Deficiency among Jaundiced Neonates: A Cross-sectional study

Running title: G6PD deficiency among Jaundiced Neonates

Zeinab A. Kasemy[1], Wael A. Bahbah[2] Sally M. El Hefnawy[3], Safa H. AlKalash[4]

1Public health and community medicine department, Menoufia faculty of medicine, Egypt

2Pediatrics department, Menoufia faculty of medicine, Egypt

3Biochemistery department, Menoufia faculty of medicine, Egypt

4Family medicine department, Menoufia faculty of medicine, Egypt

Corresponding author:

Zeinab Abdel Aziz Kasemy

Tel: +201068787807

Address: Gamal Abdel Nasser st, 5th floor, public health department, Faculty of medicine, Shibin ELkom, Menoufia, Egypt

E.mail: zeinabkasemy@yahoo.com , zeinabkasemy@gmail.com , zeinab.kasemy@med.menofia.edu.eg

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Abstract:

Objectives: To estimate the prevalence of Glucose-6-phosphate dehydrogenase (G6PD) deficiency among jaundiced neonates and assess the mothers' perception towards G6PD and Neonatal jaundice (NNJ).

Background: NNJ is a frequent complication of G6PD deficiency.

Methods: A cross-sectional study was carried out on 487 ethnic Egyptian neonates with indirect hyperbilirubinemia from June 2018 to July 2019. The collected data included maternal and neonatal characteristics. Laboratory investigations included serum bilirubin, reticulocyte count, ABO grouping, Rh typing, and neonatal serum G6PD. The mothers were interviewed individually using a structured, researcher administered questionnaire for assessing the perceptions of G6PD deficiency and NNJ.

Results: Prevalence of G6PD deficiency was 10.10%. Neonates with G6PD deficiency showed higher levels of serum bilirubin (P<0.001). Male sex, positive family history, and positive consanguinity worked as risk factors for G6PD deficiency (OR=4.27, 9.54 and10.21 respectively). Mothers' perception towards NNJ and G6PD was low towards both diseases; with only 30% have good knowledge for NNJ and 17.10% for G6PD deficiency, positive attitude (46.8% for NNJ vs. 45.0% for G6PD deficiency) and finally good practice (29.9% for NNJ vs. 19.9% for G6PD deficiency)

Conclusion: G6PD deficiency was shown to be strongly correlated with NNJ in our population; however mothers' perception of both NNJ and G6PD deficiency was low. A mass health education program about both diseases is needed to ensure better early detection, good timing treatment and better prevention of the triggering factors to ensure better health of the children.

Keywords: Awareness, G6PD deficiency, Neonatal jaundice**, Perception, Knowledge Attitude Practice, Child health, Epidemiology**

Introduction:

The term 'jaundice' is used to describe the yellow-orange discoloration of the skin and conjunctiva because of excessive bilirubin in the skin and mucous membranes. (1,2) It is not a disease, but rather a symptom or sign of a disease. (3) Jaundice (Hyperbilirubinemia) though a common benign occurrence in the 1st week of life can sometimes progress to critical levels. (4) Neonatal jaundice is a frequent complication of Glucose-6-phosphate dehydrogenase (G6PD) deficiency which is a genetic disease more often observed in males as this is X linked enzymatic deficiency but in females might present deficient activity levels which is sever enough to induce hemolysis even if they are heterozygous. (5, 6) African, Asia, Mediterranean, and Middle-Eastern descents are most commonly affected by this disorder (7, 8) Prevalence of G6PD deficiency among Egyptian neonates is (8.9%). (9) G6PD enzymatic deficiency spread from India, and its prevalence increased as it moved from place to place. (10) The deficiency itself can be triggered by specific agents like specific foods, drugs, and infections rather than the risk of hemolysis. (6) Decreasing the incidence of sever hemolysis by avoiding the triggers and early beginning of treatment including intensive phototherapy is simple and inexpensive and can be started before symptoms appear. (8, 10, 11) Counseling should be directed to parents of deficient newborns to avoid risks of jaundice and triggering agents. (10). G6PD deficiency is commonly known in Egypt as fava bean anemia or favism (after intake of fava bean) as this enzyme deficiency increases the susceptibility of red blood cells to oxidant agents such as oxidants present in raw beans, some medications and oxidative stress caused by infections .(12) There are few studies conducted about prevalence of G6PD deficiency among Egyptian jaundiced neonates (9) and also about knowledge, attitude and practice (KAP) of NNJ or G6PD Deficiency (12,13), but updating the prevalence and measuring KAP about both of NNJ and G6PD deficiency in one study is not available. So, this study aimed to estimate the prevalence of G6PD deficiency among Egyptian jaundiced neonates and assess the mothers' perception through studying their level of KAP regarding G6PD deficiency and neonatal jaundice to allow ensuring the avoidance of triggering factors.

Subjects & Methods:

A cross-sectional study was carried out in Egypt on 487 neonates with indirect hyperbilirubinemia from June 2018 to June 2019 at three Egyptian neonatal and pediatric

centers, medically serving its population and receiving patients from the surrounding areas. The studied neonates with their mothers visiting the involved pediatric and neonatal centers for seeking medical advice for treatment of jaundice were recruited from some Egyptian governorates mainly Menoufia governorate (the place of the study) and the surrounding near governorates. From 0-10 days of age with clinically evident jaundice, admitted term and preterm neonates were included in the study. The exclusion criteria included neonates with direct hyper-bilirubinemia >20% (Conjugated hyperbilirubinemia exists when more than 20% of the total bilirubin or more than 2 mg/dL is conjugated. If neither criterion is met, the hyperbilirubinemia is classified as unconjugated), metabolism errors, congenital anomalies and sepsis. All these exclusion criteria were set to be more focused on G6PD deficiency as a single cause for NNJ in this study. The collected data included maternal and neonatal characteristics in the form of gestational age (at admission), parity, gravidity, neonatal sex, weight, and jaundice age of onset (maternal recall). The studied neonates had been subjected prior to any treatment to laboratory investigations including serum bilirubin (total, direct, indirect), reticulocyte count, ABO grouping and Rh typing of the mother and baby, Coombs test (for baby only) and C reactive protein (as a routine and to exclude sepsis). UV-Kinetic Method using cellular enzyme determination reagents by spectrophotometry was used to measure quantitative estimation of serum G6PD by using 1ml of whole blood collected in an EDTA tube. Level <4.6 u/g Hb was estimated to define G6PD deficiency (9). For assessing the perception of G6PD deficiency and neonatal jaundice, the mothers of both jaundiced and non-current jaundiced neonates were interviewed individually by a trained collecting data team during admission, while the neonate receiving medical examination, using a researcher administered questionnaire. We were cautious about interviewing the mothers of the current jaundiced neonates before telling them the final diagnosis to avoid taking extra-point over the mothers of non-jaundiced ones in the final analysis of the data. The questionnaire was designed by experts in pediatrics and public health specialties based on their experience in pediatrics and public involvement besides depending on published reviews of literature. A pilot study was conducted on about 30 mothers (about 6% of the calculated sample) to test the adequacy of the questionnaire for contents, language and time consuming and to explore the potential obstacles and difficulties that confront the execution of the work in addition

to being used as a tool for training of the data collecting team (5 nurses and 3 junior staff) to avoid inter and intra-observer bias. Training was conducted with the working team for 2 days followed by testing to assess the degree of response to training and the quality of the asking and reporting. For NNJ, the questionnaire (Supplementary (Questionnaire)) included questions like mother's knowledge regarding its diagnosis, causes, complications and treatment. Regarding the attitude of mothers toward NNJ and its treatment; the questions included if the mother thinks that NNJ is a worrisome condition, etc. For practice, if she would seek medical advice. Etc. The questionnaire (Supplementary (Questionnaire)) included questions like if the mothers have ever heard about the term G6PD deficiency or the common term (fava bean anemia), in this point we continued our questions about the common term but when analyzing the data we return to the scientific term to avoid misunderstanding for the readers. The questionnaire included questions like if G6PD deficiency is a Blood disease, both parents have to be carriers for G6PD deficiency, the inheritance of G6PD deficiency related to the baby's gender, agents that can trigger an attack of G6PD deficiency like Fava beans and medications, is pallor, shortness of breath or G6PD deficiency attack is a cause of jaundice, are GIT symptoms like (nausea and vomiting) are symptoms of G6PD deficiency attack. Regarding attitude, if she sees that this is a serious problem, marriage between contagious couples is a cause, etc. Regarding practice, the questionnaire included; seeking medical advice (a general question not specifying the current condition), premarital counseling, etc.., With answers scored as correct = 1 and incorrect = 0; participants with at least 60% correct answers were considered as having good knowledge. The correct answer was determined for any single or multiple right answers in order to help estimate the final score. Participants with at least 60% positive answers were considered as having a positive attitude and practice. A health education talk was given by the researcher to the participant mothers, with adequate clarification. The study had been approved by the local ethical committee and after explanation of the study, written consent had been received from parents and caregivers.

Sample size calculation: Based on past review of literature (9) who reported that prevalence of G6PD among jaundiced newborn to be 8.9% with nearly the same inclusion and exclusion criteria included in our study, sample size has been calculated using the following equation: $n = (z^2 \times p \times q)/ D2$ at CI 95% and it was estimated to be 487 jaundiced neonates.

Statistical analysis: Data were analyzed by using SPSS version 22 (SPSS Inc., Chicago, IL, USA). Descriptive statistics in the form of percentage (%), mean ±SD and range were performed. An independent t-test and ANOVA test were used for normally distributed quantitative. Chi-square ($\chi 2$) was used for qualitative variables. Odds ratio (OR) was used to assess the risk of exposure. OR=1: Exposure does not affect odds of outcome, OR>1: Exposure associated with higher odds of outcome and OR<1: Exposure associated with lower odds of outcome. P-value less than 0.05 set to be statistically significant.

Patient and Public Involvement:

This work aimed to study the prevalence of G6PD deficiency among Egyptian jaundiced neonates and mothers' perception regarding both diseases. To improve the relevance of research, oriented research including patient and public is vital. A paper-based survey asked some mothers seeking medical advice in the three neonatal and pediatric centers to submit their unanswered questions regarding G6PD deficiency and NNJ. The final top four research priorities in an in-person meeting were ranked. Thirty respondents submitted forty questions. The respondents were from urban and rural areas. Their ages ranged from 20-40 years. The forty questions were distilled to seventeen unique questions and from this list; the top four research questions prioritized included if these diseases are infectious ones, if they can be transferred to the next generations, if they are long-life diseases and if there is a complete cure. The respondents were subjected to questionnaires by observers to assess the degree of response and reactivity. The interviewed mothers recommended to generalize the screening over large number and to be in the most crowded districts, so we asked them to tell every pregnant woman they know to seek medical advice for free in certain neonatal centers, where we are working, if there is a doubt of having a yellow baby to encourage them participate in the study. The thirty women helped us recruit about ninety two women and the rest of the sample size was based on our advertisement plus the usual patients coming to the studied centers by their own. We organized a special day at a conference meeting room to in order to thank all participants in the first place, disseminate the results and provide an in-depth group health education session about the two diseases. Special focus was directed to mothers of G6PD deficient babies to avoid triggering factors and seek medical advice promptly. For other mothers, the main aim of the health education session was to correct the wrong information and to build a base for new mothers' generation who know well these diseases and be messengers to their families and surroundings.

Results:

The study was conducted on 478 jaundiced neonates. The mothers' age ranged from 22-39 years (31.45 ±4.77). Neonates aged (0-10 days) were distributed in 69.6% males versus 30.4% females. Their birth weight ranged from (2.30-3.50 Kg). Bilirubin levels (mg/dl) were distributed into total bilirubin (mg/dl) (15.17 ±5.14), direct bilirubin (mg/dl) (1.08 ±0.38) and indirect bilirubin (mg/dl) (13.17 ±3.74). Mean Hb (gm/dl) showed a good level of about (12.18 ±1.75) despite low and high range (9.50-14.50) **(Table 1)** Prevalence of G6PD deficiency had been reported in 10.10% (<4.6 u/g Hb distributed as 42 males (2.88 ±0.95) and 7 females (4.0±0.57). (**Fig 1)** Neonates with G6PD deficiency showed higher levels of bilirubin (total, direct and indirect) (P<0.001). In this population of jaundiced neonates, G6PD deficient neonates were more likely to be of male gender (OR=4.27, CI95%: **1.66-10.99**), to be born of consanguineous parents (OR=10.21, CI 95%: 5.39-19.33) and to be of positive family history of G6PD deficiency (OR=9.54, CI 95% 4.80-18.95). **(Table 2)** Positive correlation had been noticed between G6PD and jaundice time of onset**. (Fig 2)** One of the interesting findings was that total bilirubin was higher in G6PD deficient cases (23.03 ±2.94, CI: 22.18-23.87, M=23, IQR: 21.3-25) than those with RH (15.7 ±4.75, CI: 14.33-17.12, M=15, IQR:11.6-18.2) or ABO incompatibility (11.0 ±2.59, CI: 10.49-11.79, M=11, IQR:9-13) (Fig. 3). Regarding knowledge, attitude and practice (KAP) towards NNJ and G6PD deficiency, it seems that mothers showed somehow better perception towards jaundice in comparison to G6PD deficiency, but unfortunately KAP was low towards both diseases as majority of mothers (95.9%) didn't know term (G6PD deficiency) while about 24% of them heard about fava bean anemia, also 90%of them didn't know that both parents have to be carriers for G6PD deficiency to have an affected child. All mothers knew fava beans can trigger an attack of G6PD deficiency while 39.3% knew that it is triggered by drugs **(Table 3).** Almost all mothers know about neonatal jaundice, about 70% of them thought that prematurity is a cause of neonatal jaundice, 68.6% of the mothers knew that they can detect jaundice in their newborn in skin while 25% of them reported that jaundice can be defined in sclera of newborn about 95% of the mothers knew that phototherapy is method of treatment of NJJ**.(Table 4)** Good knowledge was reported in 30% for NNJ vs. 17.10% for G6PD deficiency, positive attitude was reported in 46.8% for NNJ vs. 45.0% for G6PD deficiency and finally good practice was reported in 29.9% for NNJ vs. 19.9% for G6PD deficiency **(Fig. 4)**

Discussion:

The prevalence of G6PD deficiency was reported in 10.1% of jaundiced neonates which lied in the range of 8.9-30.2% of the prevalence of G6PD deficiency in Egyptian studies conducted in Egyptian governorates, Menoufia and Giza, which revealed that G6PD deficiency represented 8.9 % and 30.2% respectively among jaundiced newborns. (9, 13) The higher prevalence of G6PD deficiency among jaundiced neonates in El-Menshay et al., (13) may be due to nature of the chosen small sized purposive sample. This wide range could be explained by that special Egypt's geographical position between three continents with different ethnic groups results in wide variation of the prevalence of G6PD deficiency in different sectors, which is the same case on global scale where in Iraq, prevalence was 10.65% (14), in Iran, it was around 9% (15) and in South Brazil it was 7.9%. (16) Neonates with decreased G6PD showed higher levels of bilirubin and this result goes parallel to that of Bahraini and Nigerian studies conducted by Isa et al., (17) and Badejoko et al., (18) respectively. Male sex showed to be more risky to G6PD deficiency which is similar to findings reported in Egypt by Abo El Fotoh and Rizk (9), Abo Elella et al., (10) and El-Menshay et al.,(13), in India by Sinha et al., (19) and in Iran by Eghbalian and Monsef (20). Positive family history of G6PD deficiency and positive consanguinity were more at risk of acquiring G6PD deficiency which is in line with an Egyptian study conducted by Abo El Fotoh and Rizk (9) and Garg and Joag (21). On the contrary a study conducted in Japan concluded that only one case of G6PD deficiency was detected and born to non-consanguineous, Japanese parents without any family history. (22) A positive correlation between G6PD deficiency and jaundice time of onset was detected. As known, two peaks for jaundiced patients to be admitted, the first is on the 3rd day and the second is on the 7th day of life. Bimodal peaks of maximum serum bilirubin concentrations are known to happen among G6PD deficient infants and when the hemolytic episode starts early, the elevation of serum bilirubin is anticipated to be clear and hence a course of hyperbilirubinemia may, therefore, be predicted. (23) The finding is in agreement with Abo El Fotoh and Rizk (9). But it is in disagreement with result of Turkish study conducted by Atay et al., (24) In this study mean Hb (gm/dl) showed a good level of about (12.18 ±1.75) despite low and high range (9.50-14.50) and this is usual for Egyptians as the prevalence of anemia among Egyptian pregnant women is about (52.5%). (25) In G6PD-deficiency, hyperbilirubinemia in is thought to be secondary to reduced hepatic conjugation and excretion of bilirubin, rather than increased bilirubin production resulting from hemolysis. (26)

Total billirubin was obviously higher in G6PD deficient cases than those with RH or ABO incompatibility and this finding agrees with that concluded by Das and Singh (27) in India and Hussain et al., (28) in Pakistan but also in contrast to the findings obtained by Shah and Yeo (29) in Singapore and Aletayeb et al.(30) in Iran. Regarding knowledge, attitude and practice towards jaundice and G6PD, majority of mothers (95.9%) didn't know the term (G6PD deficiency) which isn't agreed with Al-Joborae, (31) who found that about 91% of mothers in Iraq heard about G6PD deficiency. In Egypt, the most commonly used term is “Fava bean anemia”, so in our study, 23% of mother heard about Fava bean anemia but 4.1% only knew the term “G6PD deficiency anemia”. All mothers knew that fava beans can trigger an attack of G6PD deficiency, hence the term came from, which is in agreement with a study carried out in Bahrain by Al Arrayed and Al Hajeri, (32). In our study, about 40% of mother thought that hemolysis can be triggered by drugs and this result is inconsistent with that obtained by Almuhaini et al., (33). Regarding mother's knowledge about neonatal jaundice, all mothers heard about it and about 40% of them reported that prematurity of the infant is a cause of its occurrence and this result is consistent with that provided by Magfouri et a., (34) in Saudi Arabia. Also in the present study, 68.6% of the mothers knew that they can detect jaundice in their newborn in the skin while 25% of them reported that jaundice can be defined in the sclera of a newborn. These findings agree with that achieved by Aggarwal et al., (35) in India. Despite of carrying out this study on a very selected group of mothers to study the KAP but really it was of benefit as most of them were experiencing for the first time a jaundiced neonate, so it seemed for us as the case of studying a group from general population besides this group will be more able to deliver the health education message as it is based on experience. It seems that mothers showed somehow better perception towards jaundice in comparison to G6PD deficiency. This is in agreement results reported by Boo et al., (36) in Malaysia. Our results still showed poor KAP regarding both diseases. This is in agreement with Goodman et al., (37) in Nigeria and Alfouwais et al., (38) in Saudi Arabia. In contrast to the study results, Al-Joborae, (31) in Iraq and Al Arrayed et al., (33) reported that the mothers had a fairly good level of awareness of G6PD deficiency. The study results showed some improvement in level of knowledge in comparison with Allahaony et al (39) who reported that only 18.9% of mothers had good knowledge, 48.0% had good attitude and only 25.3% had a good practice towards NNJ, which shows the effect of health education carried out to the mothers but it shows also that we are still in a bad need to more extensive and focused health education. The results showd that risk factors for hyperbilirubinemia

were prematurity, ABO incompatibility, and infection, which is in agreement with (Sadat et al., (40) and Rabiyeepoor, (41) in Iran.

Strengths: The study collectively assessed the prevalence and risk factors of G6PD deficiency besides assessing the level of knowledge, attitude, and practice (KAP) regarding both of G6PD deficiency and neonatal jaundice (NNJ). The study clarified the extent of change towards NNJ based on previous levels published in some research articles in the same region and also drew how much G6PD deficiency despite being a serious disease; it is a poorly known one, making a special recommendation of health education sessions for every mother to be conducted in health centers from day one. A suitable sample size had been studied in a short period, which allowed us to reach large number of mothers and families.

Limitations: There was a need to carry out more investigations to the mothers like direct Coombs test. A posttest to assess the extent of understanding and KAP among the studied mothers was needed. But it was difficult to collect this studied number one more time. We reached only the mothers who sought medical advice for their neonates. Both diseases needed KAP assessment among the general population to ensure taking care of the risk factors, but we tried to help the mothers be messengers to their families specially after conducting a health education session to thank them for participation in the study.

Conclusion: G6PD deficiency seems to be an important cause of neonatal jaundice. Cord blood for complete blood count, direct Coombs' test, blood grouping, bilirubin and G6PD screening is better to be performed in high-risk populations, to early consider a prolonged hospital stay. G6PD deficiency and NNJ are serious conditions so by studying KAP of mothers, the study revealed that mothers' KAP about NNJ despite being still low but it shows promising improvement while KAP about G6PD deficiency is so poor. So it so evitable to apply a mass health education program about both of G6PD deficiency and NNJ to ensure better early detection, good timing treatment and better prevention of the triggering factors to ensure better health of the children.

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Ethical Approval: Institutional Review Boards (IRB) of the Menoufia faculty of medicine had approved the study. Research work had been performed in accordance with the Declaration of

Helsinki. A written patient's Consent was taken after explanation of all aspects of the study and gave them the right to withdraw at any time.

Data sharing statement: Data are available to be shared on request by e. mailing zeinabkasemy@yahoo.com

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Legend of figure:

Fig 1: Prevalence of G6PD deficiency among the studied jaundiced neonate group

Fig 2: Correlation between G6PD and Jaundice time of onset in deficient cases

Fig 3: Total bilirubin distribution among patients with G6PD deficiency, RH incompatibility and ABO incompatibility

Fig 4: Perception of G6PD deficiency and neonatal jaundice among the studied mothers

Table 1: General characteristics of the studied mothers and jaundiced neonates:

General characteristics	Study group (n=487)	
Mothers' characteristics		
Age (Y) (Mean ±SD, range)	31.45±4.77	22-39
Gestational age(week) (Mean ±SD, range)	37.71±1.05	37-41
BMI(kg/m2) (Mean ±SD, range)	22.02 ±2.37	18.30-27.10
Gravidity no,%		
≤3	292	60.0
>3	195	40.0
Parity no,%		
≤2	252	51.7
>2	235	48.3
Neonatal characteristics		
Sex: no,%		
Male	339	69.6
Female	148	30.4
Birth weight (kg) (Mean ±SD, range)	2.60±0.29	2.30-3.50
Age of neonate(days) (Mean ±SD, range)	4.45 ±0.86	3-8
Bilirubin(mg/dl) (Mean ±SD, range)		
• Total	15.17 ±5.14	7.30-25.50
• Direct	1.08±0.38	1.50-0.50
• Indirect	13.17 ±3.74	6.40-23.15
Hb (gm/dl) (Mean ±SD, range)	12.18 ±1.75	9.50-14.50
Reticulocyte count (%)(Mean ±SD, range)	3.38 ±1.30	1.40-6.0
Age of onset of jaundice (Maternal recall) (Mean ±SD, range)	3.45±0.85	2-7
Need for Phototherapy on admission (no,%)	5	0.20
+ve Family history of G6PD (no,%)	144	29.6
+ve Consanguinity (no,%)	103	21.1
ABO incompatibility	63	12.9
Rh incompatibility	47	9.7

Table 2: Distribution of the studied G6PD groups regarding bilirubin, neonate sex, family history and consanguinity:

	G6PD						
	Deficient No.=49 mean ±SD		Normal No. =438 mean ±SD		Test of sig	P value	OR CI 95%
Bilirubin(mg/dl)							
• **Total**	23.0 3±2.94		14.30 ±4.55		**t=18.40**	**<0.001***	**-**
• **Direct**	1.38 ±0.14		1.02 ±0.41		**t=12.47**	**<0.001***	
• **Indirect**	17.02 ±3.45		12.74 ±3.52		**t=8.21**	**<0.001**	
Neonate Sex	no	%	no	%			
Male	42	85.7	297	45.0	**χ^2=10.49**	**0.001***	**4.27(1.66-10.99)**
Female	7	14.3	141	55.0			**1.0**
Family history of G6PD deficiency							
+ve	37	75.5	107	24.4	**χ^2=55.21**	**<0.001***	**9.54(4.80-18.95)**
-ve	12	24.5	331	75.6			**1.0**
Consanguinity							
+ve	33	67.3	70	16.0	**χ^2=69.72**	**<0.001***	**10.21(5.39-19.33)**
-ve	16	32.7	368	84.0			**1.0**

***Significant, family history: not in the current family but in their relatives**

Table 3: Knowledge, attitude and practice of the studied mothers regarding G6PD deficiency:

Knowledge	No.=487 no	%
Hearing about G6PD deficiency (per say)		
- Yes	2	4.1
- No	485	95.9
Hearing about fava bean anemia (G6PD Deficiency)		
• Yes	112	23.0
• No	375	76.0
G6PD deficiency is a blood disease		
- Yes	100	89.3
- No	12	10.7
- I don't know	0	0.0
Is it a hereditary disease:		
• Yes	105	93.8
• No	5	4.5
• I don't know	2	1.8
Both parents have to be carriers for G6PD deficiency to have an affected child?		
- Yes	5	4.5
- No	1	0.9
- I don't know	101	90.2
The inheritance of G6PD deficiency related to the baby's gender?		
- Yes	10	8.9
- No	3	2.7
- I don't know	99	88.4
Knowing whether personally you may have a G6PD deficiency child		
- Yes	8	7.1
- No	85	75.9
- I don't know	29	25.9
There should be a family history of G6PD deficiency to result	75	67.0
- Yes	15	13.4
- No	62	55.4
- I don't know		
Some medications Can trigger an attack of G6PD deficiency	44	39.3
• Yes	10	8.9
• No	58	51.8
• I don't know		
Symptoms of G6PD attack:	10	8.9
Pallor	52	46.4
• Yes	60	53.8
• No		
• I don't know		
Nausea, vomiting, anorexia and diarrhea		
• Yes	15	13.4
• No	45	40.2
• I don't know	52	46.4
Dizziness		
• Yes	30	26.8
• No	5	4.5
• I don't know	77	68.8
Shortness of breath		
• Yes	35	31.3
• No	5	4.5
I don't know	72	66.1
G6PD is a cause of Jaundice		
• Yes	105	93.8
• No	2	1.8
• I don't know	5	4.5

Attitude	no	%
Is this a serious problem		
- Yes	100	89.3
- No	5	4.5
- I don't know	7	6.3
Consanguinity is the cause of the disease		
- Yes	40	35.7
- No	20	17.9
I don't know	52	4.3
Next pregnancy should be prevented:		
- Yes	3	2.7
- No	50	44.6
- I don't know	59	52.7
Follow-up of the diseased child should continue for life	100	89.3
- Yes	2	1.8
- No	10	8.9
- I don't know		

Practice	no	%
Have you been subjected to premarital counseling	112	100.0
- Yes	0	0.0
- No		
Have you been subjected to genetic screening		
- Yes	2	1.8
- No	110	98.2
- I don't know	0	0.0
Seeking medical advice after delivery to be assured	0	0.0
- Yes	112	100.0
- No		

Table 4: Knowledge, attitude and practice of the studied mothers regarding NNJ:

No.=487					
Knowledge	**no**	**%**	**Attitude**	**no**	**%**
Hearing of NNJ			NNJ is a worrisome condition?		
Yes	487	100.0	- Yes	248	50.9
No	0	0.0	- No	200	41.1
Site to detect NNJ			- I don't know	39	8.0
Skin	334	68.6	Phototherapy is the best way in treatment		
Eye	123	25.2	- Yes	409	84
Tongue	30	6.2	- No	8	1.6
Causes			- I don't know	70	14.4
Prematurity	341	70.0	Blood exchange transfusion is the best way of management	107	22
ABO disparity between mother and baby	73	15.0	- Yes	50	10.3
Breastfeeding	146	30.0	- No	330	67.7
Infection	139	33.0	- I don't know		
Hemolysis	194	39.8	Is it important seeking medical advice		
Dehydration	170	34.9	- Yes	450	92.4
Increased U/S examination during pregnancy	292	60.0	- No	20	4.1
Diabetic mothers	73	15.0	- I don't know	18	13.5
Others	141	28.9			
Complications					
Death	146	30.0	**Practice**	**no**	**%**
Cerebral palsy	112	23.0	**Seeking quickly medical advice if having baby with NNJ**		
Mental retardation	170	34.9	- Yes	477	95.9
Handicapping	112	23.0	- No	10	4.1
Hearing loss	30	6.2	- I don't know	0	0.0
			Causes of denial of medical care :	N=10	
Methods of treatment			- Afraid of hospitalization.	6	60.0
Phototherapy	461	94.7	- Admission/ investigation not required.	**1**	10.0
Blood exchange transfusion	146	30.0	- High cost of medical care.	2	20.0
Drugs	399	82.0	- Lack of transportation.	0	0.0
Neon lamp	364	74.7	- Long hours to reach hospital.	0	0.0
Increase breastfeeding	238	48.9	**Time of seeking medical advice**		
			- Within 24-48 h	136	28.5
			- >48 h	341	71.5
			Continuation of breastfeeding		
			- Yes	448	92.0
			- No	39	8.0

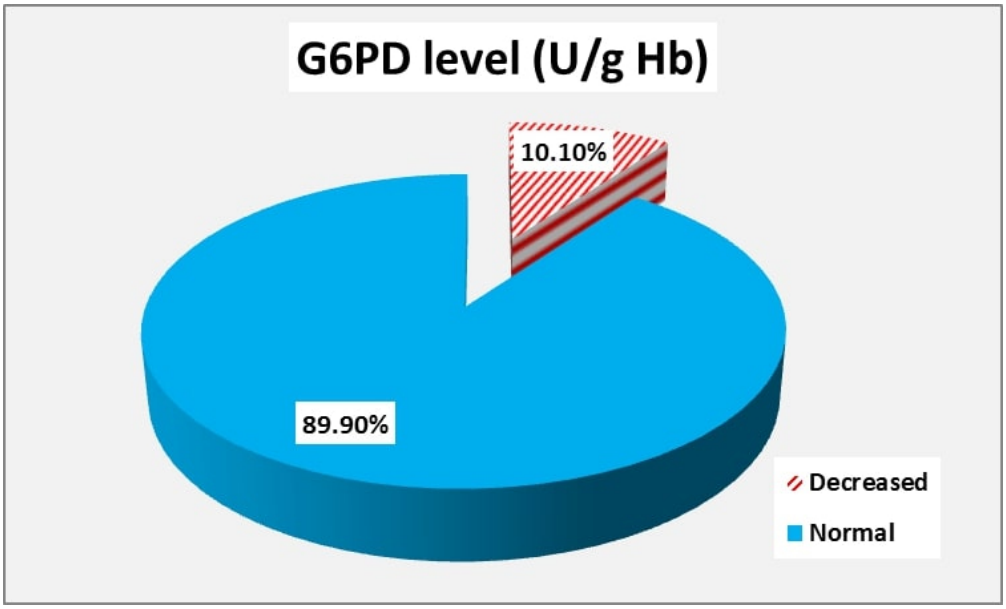

Fig 1: Prevalence of G6PD deficiency among the studied jaundiced neonate group

63x38mm (300 x 300 DPI)

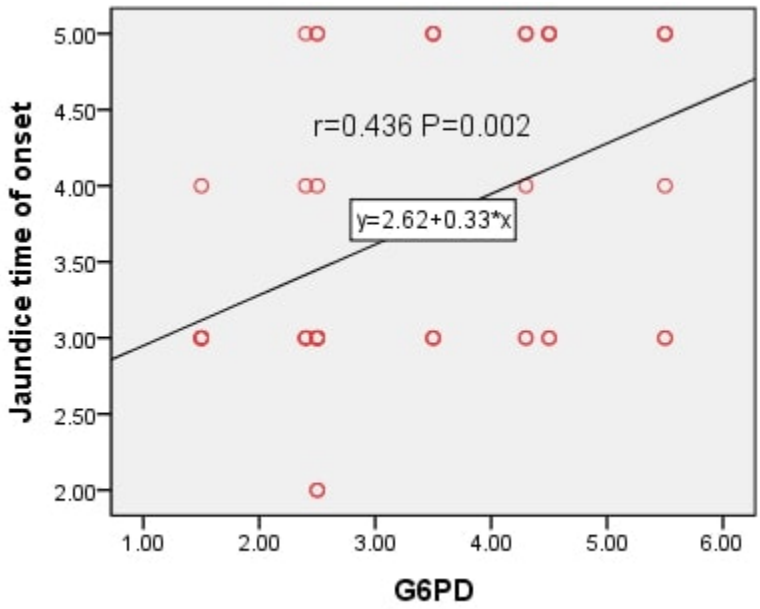

Fig 2: Correlation between G6PD and Jaundice time of onset in deficient cases

33x26mm (300 x 300 DPI)

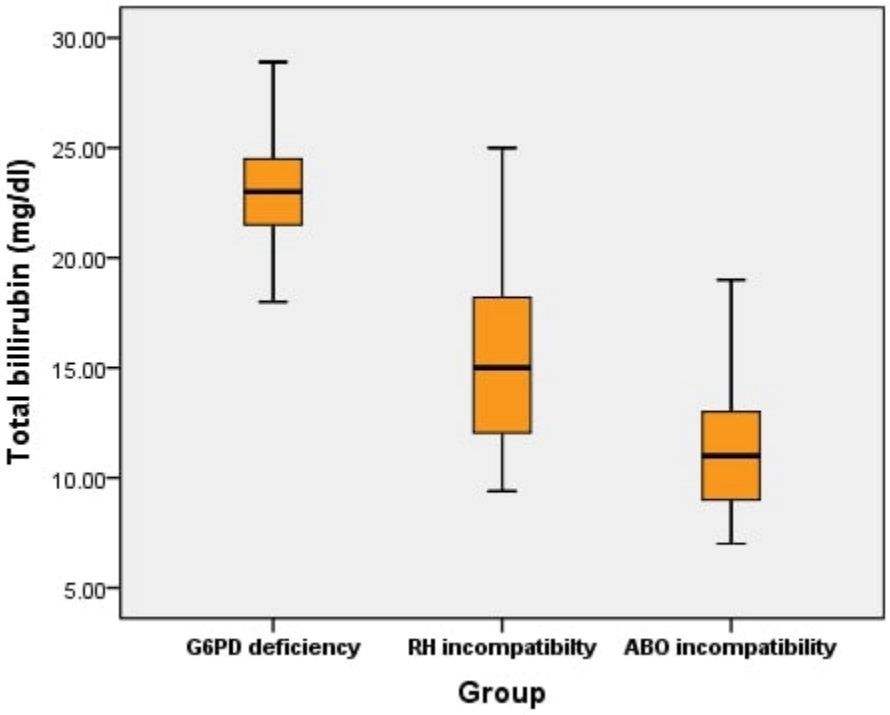

Fig 3: Total bilirubin distribution among patients with G6PD deficiency, RH incompatibility and ABO incompatibility

38x31mm (300 x 300 DPI)

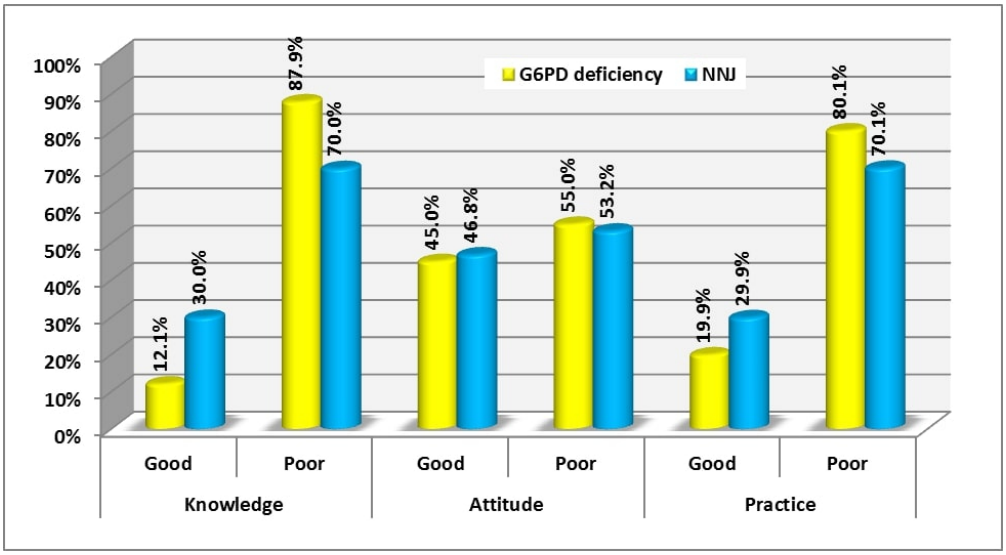

Fig 4: Knowledge, attitude and practice of G6PD deficiency and neonatal jaundice among the studied mothers

82x45mm (300 x 300 DPI)

Questionnaire for assessing Prevalence and Mothers' knowledge, attitude and practice of G6PD Deficiency among Jaundiced Neonates

Mothers' characteristics			
Age (Y):	**Gestational age(week):**	**Wight (cm):**	**Height** (kg):
Gravidity:	**Parity:**		

Neonatal characteristics		
Sex: Male Female		
Birth weight (kg):	**Age of neonate(days):**	**Age of onset of jaundice:**
Need for Phototherapy on admission	**+ve**	**-ve**
Family history of G6PD deficiency	**+ve**	**-ve**
Consanguinity	**+ve**	**-ve**

Lab investigation:	
Bilirubin(mg/dl) • Total • Direct • Indirect	• Hb (gm/dl) • Reticulocyte count • ABO incompatibility • Rh incompatibility
G6PD (u/g Hb):	

Knowledge, attitude and practice of the studied mothers regarding G6PD deficiency:

- **Have you heard about G6PD deficiency (Per say)?**
  -Yes
  -No
- **Have you heard about fava bean anemia (G6PD deficiency)?**
  -Yes
  -No
- **Is fava bean anemia (G6PD deficiency) a blood disease?**
  -Yes
  -No
  -I don't know
- **Is it a hereditary disease:**
  -Yes
  -No
  -I don't know
- **Do both parents have to be carriers for fava bean anemia (G6PD deficiency) to get an affected child?**
  -Yes
  -No
  -I don't know
- **Is the inheritance related to the baby's gender?**
  -Yes
  -No
  -I don't know
- **Do you know whether personally you may have a fava bean anemia (G6PD deficiency) child?**
- Yes
- No
- I don't know
- **Is the family history of fava bean anemia (G6PD deficiency) a condition for occurrence of the disease?**
  -Yes
  -No
  -I don't know
- **Can some medications trigger an attack of fava bean anemia (G6PD deficiency)?**
  -Yes
  -No
  -I don't know
- **Is pallor a symptom of fava bean anemia (G6PD deficiency) attack?**
  -Yes

-No
-I don't know

- **May nausea, vomiting, anorexia and diarrhea be symptoms of fava bean anemia (G6PD deficiency) attack?**
-Yes
-No
-I don't know
- **May dizziness be a symptom of fava bean anemia (G6PD deficiency) attack?**
- Yes
- No
- I don't know
- **May shortness of breath be a symptom of fava bean anemia (G6PD deficiency) attack?**
- Yes
- No
- I don't know
- **Is fava bean anemia (G6PD deficiency) a cause of Jaundice?**
- Yes
- No
- I don't know

Attitude

- **Is fava bean anemia (G6PD deficiency) a serious problem?**
- Yes
- No
- I don't know
- **Is consanguinity a cause of the disease?**
- Yes
- No
- I don't know
- **Should next pregnancy be prevented if there is one child has the disease within the family?**
- Yes
- No
- I don't know
  - **Should follow-up of the diseased child continue for life?**
- Yes
- No
- I don't know

Practice

- **Have you been subjected to premarital counseling?**
- Yes
- No
- **Have you been subjected to genetic screening?**
- Yes
- No
- I don't know
- **Do you seek medical advice after delivery to be assured?**
- Yes
- No

Knowledge, attitude and practice of the studied mothers regarding NNJ:

- **Have you heard about neonatal jaundice?** Yes No
- **What are sites of detection of neonatal jaundice**?
- Skin
- Eye
- Tongue
- **What are causes of neonatal jaundice**?
- Prematurity
- ABO disparity between mother and baby

- Breastfeeding
- Infection
- Hemolysis
- Dehydration
- Increased U/S examination during pregnancy
- Diabetic mothers
- Others

○ **What are complications of neonatal jaundice**?

- Death
- Cerebral palsy
- Mental retardation
- Handicapping
- Hearing loss

○ **What are methods of treatment of neonatal jaundice**?

- Phototherapy
- Blood exchange transfusion
- Drugs
- Neon lamp
- Increase breastfeeding

Attitude

○ **Is neonatal jaundice a worrisome condition?**

- Yes
- No
- I don't know

○ **Is phototherapy the best way in treatment?**

- Yes
- No
- I don't know

○ **Is blood exchange transfusion the best way of management?**

- Yes
- No
- I don't know

○ **Is it important seeking medical advice?**

- Yes
- No
- I don't know

Practice

○ **Do you seek a medical advice quickly if having baby with NNJ**

- Yes
- No
- I don't know

○ **If no why?**

- Afraid of hospitalization.
- Admission/ investigation not required.
- High cost of medical care.
- Lack of transportation.
- Long hours to reach hospital**.**

○ **When do you seek a medical advice?**

- Within 24-48 h
- >48h

○ **Will you continue breastfeeding?**

- Yes
- No

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any pre-specified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	3
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	4
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4-5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*4-5*
Bias	9	Describe any efforts to address potential sources of bias	10
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5
		(*b*) Describe any methods used to examine subgroups and interactions	5
		(*c*) Explain how missing data were addressed	-
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	-

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	5-6
		(b) Indicate number of participants with missing data for each variable of interest	-
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	-
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	-
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	-
		Cross-sectional study—Report numbers of outcome events or summary measures	-
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	-
		(*b*) Report category boundaries when continuous variables were categorized	-
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	7
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	-
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	7-8-9
Generalisability	21	Discuss the generalisability (external validity) of the study results	9-10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.
Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Prevalence and Mothers' Knowledge, Attitude and practice of Glucose-6-Phosphate Dehydrogenase Deficiency among Jaundiced Neonates: A cross-sectional study

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Prevalence and Mothers' Knowledge, Attitude and practice of Glucose-6-Phosphate Dehydrogenase Deficiency among Jaundiced Neonates: A Cross-sectional study

Running title: G6PD deficiency among Jaundiced Neonates

Zeinab A. Kasemy[1], Wael A. Bahbah[2] Sally M. El Hefnawy[3], Safa H. AlKalash[4]

1Public health and community medicine department, Menoufia faculty of medicine, Egypt

2Pediatrics department, Menoufia faculty of medicine, Egypt

3Biochemistery department, Menoufia faculty of medicine, Egypt

4Family medicine department, Menoufia faculty of medicine, Egypt

Corresponding author:

Zeinab Abdel Aziz Kasemy

Tel: +201068787807

Address: Gamal Abdel Nasser st, 5th floor, public health department, Faculty of medicine, Shibin ELkom, Menoufia, Egypt

E.mail: zeinabkasemy@yahoo.com , zeinabkasemy@gmail.com , zeinab.kasemy@med.menofia.edu.eg

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Strengths:

- The study collectively assessed the prevalence and risk factors of G6PD deficiency besides assessing the level of knowledge, attitude, and practice (KAP) regarding both of G6PD deficiency and neonatal jaundice (NNJ).
- The study clarified the extent of change towards NNJ based on previous levels published in some research articles in the same region and also drew how much G6PD deficiency despite being a serious disease; it is a poorly known one.
- A suitable sample size had been studied in a short period, which allowed us to reach large number of mothers and families.

Limitations:

- There was a need to carry out more investigations to the mothers like direct Coombs test.
- A posttest to assess the extent of understanding and KAP among the studied mothers was needed. But it was difficult to collect this studied number one more time. Both diseases need KAP assessment among the general population to ensure taking care of the risk factors, but we tried to help the mothers be messengers to their families specially after conducting a health education session to thank them for participation in the study.

Abstract:

Objectives: To estimate the prevalence of Glucose-6-phosphate dehydrogenase (G6PD) deficiency among jaundiced neonates and assess the mothers' perception towards G6PD and Neonatal jaundice (NNJ).

Background: NNJ is a frequent complication of G6PD deficiency.

Methods: A cross-sectional study was carried out on 487 ethnic Egyptian neonates with indirect hyperbilirubinemia from June 2018 to July 2019. The collected data included maternal and neonatal characteristics. Laboratory investigations included serum bilirubin, reticulocyte count, ABO grouping, Rh typing, and neonatal serum G6PD. The mothers were interviewed individually using a structured, researcher administered questionnaire for assessing the perceptions of G6PD deficiency and NNJ.

Results: Prevalence of G6PD deficiency was 10.10%. Neonates with G6PD deficiency showed higher levels of serum bilirubin (P<0.001). Male sex, family history of G6PD deficiency, and consanguinity worked as risk factors for G6PD deficiency (OR=4.27(95%CI: **1.66-10.99)**, 9.54 (95%CI: **4.80-18.95)** and 10.219(5%CI: **5.39-19.33)** respectively). Mothers' perception towards NNJ and G6PD was low towards both diseases; with only 30% have good knowledge for NNJ and 17.10% for G6PD deficiency, positive attitude (46.8% for NNJ vs. 45.0% for G6PD deficiency) and finally good practice (29.9% for NNJ vs. 19.9% for G6PD deficiency)

Conclusion: G6PD deficiency seems to be an important cause of neonatal jaundice. Mothers' perception of both NNJ and G6PD deficiency was low. A mass health education program about both diseases is needed to ensure better early detection, good timing treatment and better prevention of the triggering factors to ensure better health of the children.

Keywords: Awareness, G6PD deficiency, Neonatal jaundice**, Perception, Knowledge Attitude Practice, Child health, Epidemiology**

Introduction:

The term 'jaundice' is used to describe the yellow-orange discoloration of the skin and conjunctiva because of excessive bilirubin in the skin and mucous membranes. (1,2) It is not a disease, but rather a symptom or sign of a disease. (3) Jaundice (Hyperbilirubinemia) though a common benign occurrence in the 1st week of life can sometimes progress to critical levels. (4) Neonatal jaundice is a frequent complication of Glucose-6-phosphate dehydrogenase (G6PD) deficiency which is a genetic disease more often observed in males as this is X linked enzymatic deficiency but in females might present deficient activity levels which is sever enough to induce hemolysis even if they are heterozygous. (5, 6) African, Asia, Mediterranean, and Middle-Eastern descents are most commonly affected by this disorder (7, 8) Prevalence of G6PD deficiency among Egyptian neonates is (8.9%). (9) G6PD enzymatic deficiency was first reported in India, and its prevalence changes greatly from place to place. (10) The hemolysis in G6PD deficiency patients can be triggered by specific agents like specific foods, drugs, and infections rather. (6) Decreasing the incidence of sever hemolysis by avoiding the triggers and early beginning of treatment including intensive phototherapy is simple and inexpensive and can be started before symptoms appear. (8, 10, 11) Counseling should be directed to parents of deficient newborns to avoid risks of jaundice and triggering agents. (10). G6PD deficiency is commonly known in Egypt as fava bean anemia or favism (after intake of fava bean) as this enzyme deficiency increases the susceptibility of red blood cells to oxidant agents such as oxidants present in raw beans, some medications and oxidative stress caused by infections .(12) There are few studies conducted about prevalence of G6PD deficiency among Egyptian jaundiced neonates (9) and also about knowledge, attitude and practice (KAP) of NNJ or G6PD Deficiency (12,13), but updating the prevalence and measuring KAP about both of NNJ and G6PD deficiency in one study is not available. So, this study aimed to estimate the prevalence of G6PD deficiency among Egyptian jaundiced neonates and assess the mothers' perception through studying their level of KAP regarding G6PD deficiency and neonatal jaundice to allow ensuring the avoidance of triggering factors.

Subjects & Methods:

A cross-sectional study was carried out in Egypt on 487 neonates with indirect hyperbilirubinemia from June 2018 to June 2019 at three Egyptian neonatal and pediatric

centers, medically serving its population and receiving patients from the surrounding areas. The studied neonates with their mothers visiting the involved pediatric and neonatal centers for seeking medical advice for treatment of jaundice were recruited from some Egyptian governorates mainly Menoufia governorate (the place of the study) and the surrounding near governorates. From 0-10 days of age with clinically evident jaundice, admitted term and preterm neonates were included in the study. The exclusion criteria included neonates with direct hyper-bilirubinemia >20% (Conjugated hyperbilirubinemia exists when more than 20% of the total bilirubin or more than 2 mg/dL is conjugated. If neither criterion is met, the hyperbilirubinemia is classified as unconjugated), metabolism errors, congenital anomalies and sepsis. All these exclusion criteria were set to be more focused on G6PD deficiency as a single cause for NNJ in this study. The collected data included maternal and neonatal characteristics in the form of gestational age (at admission), parity, gravidity, neonatal sex, weight, and jaundice age of onset (maternal recall). The studied neonates had been subjected prior to any treatment to laboratory investigations including serum bilirubin (total, direct, indirect), reticulocyte count, ABO grouping and Rh typing of the mother and baby, Coombs test (for baby only) and C reactive protein (as a routine and to exclude sepsis). UV-Kinetic Method using cellular enzyme determination reagents by spectrophotometry was used to measure quantitative estimation of serum G6PD by using 1ml of whole blood collected in an EDTA tube. Level <4.6 u/g Hb was estimated to define G6PD deficiency (9). The studied neonates were subjected to phototherapy according to guidelines of phototherapy in hospitalized infants from ≥35 weeks of gestation (14). For assessing the perception of G6PD deficiency and neonatal jaundice, the mothers of both jaundiced (n=487) and non-current jaundiced neonates (n=3) excluded from the study due to very small number) were interviewed individually by a trained collecting data team during admission, while the neonate receiving medical examination, using a researcher administered questionnaire. We were cautious about interviewing the mothers of the current jaundiced neonates before telling them the final diagnosis to avoid taking extra-point over the mothers of non-jaundiced ones in the final analysis of the data. The questionnaire was designed by experts in pediatrics and public health specialties based on their experience in pediatrics and public involvement besides depending on published reviews of literature. A pilot study was conducted on about 30 mothers (about 6% of the

calculated sample) to test the adequacy of the questionnaire for contents, language and time consuming and to explore the potential obstacles and difficulties that confront the execution of the work in addition to being used as a tool for training of the data collecting team (5 nurses and 3 junior staff) to avoid inter and intra-observer bias. Training was conducted with the working team for 2 days followed by testing to assess the degree of response to training and the quality of the asking and reporting. For NNJ, the questionnaire (Supplementary (Questionnaire)) included questions like mother's knowledge regarding its diagnosis, causes, complications and treatment. Regarding the attitude of mothers toward NNJ and its treatment; the questions included if the mother thinks that NNJ is a worrisome condition, etc. For practice, if she would seek medical advice. Etc. The questionnaire (Supplementary (Questionnaire)) included questions like if the mothers have ever heard about the term G6PD deficiency or the common term (fava bean anemia), in this point we continued our questions about the common term but when analyzing the data we return to the scientific term to avoid misunderstanding for the readers. The questionnaire included questions like if G6PD deficiency is a Blood disease, both parents have to be carriers for G6PD deficiency, the inheritance of G6PD deficiency related to the baby's gender, agents that can trigger an attack of G6PD deficiency like Fava beans and medications, is pallor, shortness of breath or G6PD deficiency attack is a cause of jaundice, are GIT symptoms like (nausea and vomiting) are symptoms of G6PD deficiency attack. Regarding attitude, if she sees that this is a serious problem, marriage between contagious couples is a cause, etc. Regarding practice, the questionnaire included; seeking medical advice (a general question not specifying the current condition), premarital counseling, etc.., With answers scored as correct = 1 and incorrect = 0; participants with at least 60% correct answers were considered as having good knowledge. The correct answer was determined for any single or multiple right answers in order to help estimate the final score. Participants with at least 60% positive answers were considered as having a positive attitude and practice. A health education talk was given through an organized special day at a conference meeting room by the researcher to the participant mothers, with adequate clarification. The study had been approved by the local ethical committee and after explanation of the study, written consent had been received from parents and caregivers.

Sample size calculation: Based on past review of literature (9) who reported that prevalence of G6PD among jaundiced newborn to be 8.9% with nearly the same inclusion and exclusion criteria included in our study, sample size has been calculated using the following equation: n = ($z^2 \times p \times q$)/ D2 at CI 95% and it was estimated to be 487 jaundiced neonates.

Statistical analysis: Data were analyzed by using SPSS version 22 (SPSS Inc., Chicago, IL, USA). Descriptive statistics in the form of percentage (%), mean ±SD and range were performed. An independent t-test and ANOVA test were used for normally distributed quantitative. Chi-square ($\chi 2$) was used for qualitative variables. Odds ratio (OR) was used to assess the risk of exposure. OR=1: Exposure does not affect odds of outcome, OR>1: Exposure associated with higher odds of outcome and OR<1: Exposure associated with lower odds of outcome. Pearson's correlation was used to assess direction and strength of association between variables. P-value less than 0.05 set to be statistically significant.

Patient and Public Involvement:

This work aimed to study the prevalence of G6PD deficiency among Egyptian jaundiced neonates and mothers' perception regarding both diseases. To improve the relevance of research, oriented research including patient and public is vital. A paper-based survey asked some mothers seeking medical advice in the three neonatal and pediatric centers to submit their unanswered questions regarding G6PD deficiency and NNJ. The final top four research priorities in an in-person meeting were ranked. Thirty respondents submitted forty questions. The respondents were from urban and rural areas. Their ages ranged from 20-40 years. The forty questions were distilled to seventeen unique questions and from this list; the top four research questions prioritized included if these diseases are infectious ones, if they can be transferred to the next generations, if they are long-life diseases and if there is a complete cure. The respondents were subjected to questionnaires by observers to assess the degree of response and reactivity. The interviewed mothers recommended to generalize the screening over large number and to be in the most crowded districts, so we asked them to tell every pregnant woman they know to seek medical advice for free in certain neonatal centers, where we are working, if there is a doubt of having a yellow baby to encourage them participate in the study. The thirty women helped us recruit about ninety two women and the rest of the sample size was based on our advertisement plus the usual patients coming to the studied centers by their own. We organized a special day at a conference meeting room to in order to thank all participants in the first place, disseminate the results and provide an in-depth group health education session about the two diseases. Special

focus was directed to mothers of G6PD deficient babies to avoid triggering factors and seek medical advice promptly. For other mothers, the main aim of the health education session was to correct the wrong information and to build a base for new mothers' generation who know well these diseases and be messengers to their families and surroundings.

Results:

The study was conducted on 478 jaundiced neonates. The mothers' age ranged from 22-39 years (31.45 ±4.77). Neonates aged (0-10 days) were distributed in 69.6% males versus 30.4% females. Their birth weight ranged from (2.30-3.50 Kg). Bilirubin levels (mg/dl) were distributed into total bilirubin (mg/dl) (15.17 ±5.14), direct bilirubin (mg/dl) (1.08 ±0.38) and indirect bilirubin (mg/dl) (13.17 ±3.74). Mean Hb (gm/dl) showed a good level of about (12.18 ±1.75) despite low and high range (9.50-14.50). The total percentage of the jaundiced neonates needed phototherapy on admission was 4.7%. G6PD deficient cases needed phototherapy on admission represented about 0.20% of the total jaundiced neonates. Family history of G6PD deficiency and consanguinity were reported among 29.6% and 21.1% respectively. ABO incompatibility and Rh incompatibility were detected in 12.9% and 9.7% respectively. **(Table 1)** Prevalence of G6PD deficiency had been reported in 10.10% (<4.6 u/g Hb distributed as 42 males (2.88 ±0.95) and 7 females (4.0±0.57). (**Fig 1)** Neonates with G6PD deficiency showed higher levels of bilirubin (total, direct and indirect) (P<0.001). In this population of jaundiced neonates, G6PD deficient neonates were more likely to be of male gender (OR=4.27, CI95%: **1.66-10.99**), to be born of consanguineous parents (OR=10.21, CI 95%: 5.39-19.33) and to be of positive family history of G6PD deficiency (OR=9.54, CI 95% 4.80-18.95). **(Table 2)** Positive correlation had been noticed between G6PD level among G6PD deficient neonates and jaundice time of onset based on maternal recall (r=0.436, P=0.002)**.** One of the interesting findings was that total bilirubin was higher in G6PD deficient cases (23.03 ±2.94, CI: 22.18-23.87, M=23, IQR: 21.3-25) than those with RH (15.7 ±4.75, CI: 14.33-17.12, M=15, IQR: 11.6-18.2) or ABO incompatibility (11.0 ±2.59, CI: 10.49-11.79, M=11, IQR: 9-13) **(Fig. 2).** Regarding knowledge, attitude and practice (KAP) towards NNJ and G6PD deficiency, it seems that mothers showed somehow better perception towards jaundice in comparison to G6PD deficiency, but unfortunately KAP was low towards both diseases as majority of mothers (95.9%) didn't know term (G6PD deficiency) while about 24% of them heard about fava bean anemia, also 90%of them didn't know that parents

(both or just the mother) have to be carriers for G6PD deficiency to have an affected child. All mothers knew fava beans can trigger an attack of G6PD deficiency while 39.3% knew that it is triggered by drugs **(Table 3).** Almost all mothers know about neonatal jaundice, about 70% of them thought that prematurity is a cause of neonatal jaundice, 68.6% of the mothers knew that they can detect jaundice in their newborn in skin while 25% of them reported that jaundice can be defined in sclera of newborn about 95% of the mothers knew that phototherapy is method of treatment of NJJ**.(Table 4)** Good knowledge was reported in 30% for NNJ vs. 17.10% for G6PD deficiency, positive attitude was reported in 46.8% for NNJ vs. 45.0% for G6PD deficiency and finally good practice was reported in 29.9% for NNJ vs. 19.9% for G6PD deficiency **(Fig. 3)**

Discussion:

The prevalence of G6PD deficiency was reported in 10.1% of jaundiced neonates which lied within the range of the prevalence revealed in some Egyptian studies (8.9-30.2%). (9, 13) The higher prevalence of G6PD deficiency among jaundiced neonates (30.2%) in El-Menshay et al., (13) may be due to the small sized purposive sample chosen for conducting the study. The wide range of G6PD deficiency prevalence in Egypt could be explained by Egypt's special geographical position between three continents with different ethnic groups, which is the same case on global scale where in Iraq, prevalence was 10.65% (15), in Iran, it was around 9% (16) and in South Brazil it was 7.9%. (17) Neonates with G6PD deficiency showed higher levels of bilirubin and this result goes parallel to that of Bahraini and Nigerian studies conducted by Isa et al., (18) and Badejoko et al., (19) respectively. Male sex showed to be more risky to G6PD deficiency which is similar to findings reported in Egypt by (Abo El Fotoh and Rizk (9), Abo Elella et al., (10) and El-Menshay et al.,(13)), in India by Sinha et al., (20) and in Iran by Eghbalian and Monsef (21). Family history of G6PD deficiency and consanguinity are risk factors for acquiring G6PD deficiency which coincide with an Egyptian study conducted by Abo El Fotoh and Rizk (9) and Garg and Joag (22). On the contrary, a study conducted in Japan stated that only one case of G6PD deficiency was born to non-consanguineous Japanese parents without any family history. (23) A positive correlation between G6PD deficiency and jaundice time of onset (based on maternal recall) was detected. As known, two peaks for jaundiced patients to be admitted, the first is on the 3rd day and the second is on the 7th day of life. Bimodal peaks of maximum serum bilirubin concentrations are known to happen among G6PD deficient infants and when the hemolytic episode starts early, the elevation of serum bilirubin is

anticipated to be clear and hence a course of hyperbilirubinemia may, therefore, be predicted. (24) The finding is in accordance with Abo El Fotoh and Rizk (9). But it is in disagreement with Turkish study conducted by Atay et al., (25). Mean Hb (gm/dl) showed a good level of about (12.18 ±1.75) despite the low and high range (9.50-14.50) and this is usual for Egyptians as the prevalence of anemia among Egyptian pregnant women is about (52.5%). (26) The total percentage of the jaundiced neonates needed phototherapy on admission was 4.7%. G6PD deficient cases needed phototherapy on admission represented about 0.20% of the total jaundiced neonates. The studied neonates were subjected to phototherapy according to guidelines of phototherapy in hospitalized infants from ≥35 weeks of gestation (14). In G6PD-deficiency, hyperbilirubinemia is thought to be secondary to reduced hepatic conjugation and excretion of bilirubin, rather than increased bilirubin production resulting from hemolysis. (27) Total billirubin was obviously higher among G6PD deficient cases than those with RH or ABO incompatibility and this finding agrees with that concluded by Das and Singh (28) in India and Hussain et al., (29) in Pakistan but also in contrast to the findings obtained by Shah and Yeo (30) in Singapore and Aletayeb et al. (31) in Iran. Knowledge, attitude and practice towards G6PD deficiency showed that majority of mothers (95.9%) didn't know the term (G6PD deficiency) which doesn't agree with Al-Joborae, (32) who found that about 91% of mothers in Iraq heard about G6PD deficiency. In Egypt, the most commonly used term is “Fava bean anemia”, so in our study, 23% of mother heard about Fava bean anemia but 4.1% only knew the term “G6PD deficiency anemia”. All mothers knew that fava beans can trigger an attack of hemolysis due to G6PD deficiency, hence the term came from, and this is in agreement with a study carried out in Bahrain by Al Arrayed and Al Hajeri, (33). In this study, about 40% of mothers thought that hemolysis can be triggered by drugs and this result is inconsistent with that obtained by Almuhaini et al., (34). The current study revealed that all mothers have heard about NNJ and about 70% of them reported that prematurity of the infant is a cause of its occurrence and this result is consistent with Magfouri et al., (35) in Saudi Arabia. Jaundice can be detected in the skin and sclera by 68.6% and 25% of the mothers respectively. These findings agree with that achieved by Aggarwal et al., (36) in India. Despite of carrying out this study on a very selected group of mothers to study the KAP but really it was of benefit as most of them were experiencing a jaundiced neonate for the first time, so it seemed for us as the case of studying of a group of general population, besides this group will be more able to deliver the health

education message as it is based on self-experience. Mothers showed somehow better perception towards jaundice in comparison to G6PD deficiency. This is in agreement with results reported by Boo et al., (37) in Malaysia. Our results still showed poor KAP regarding both diseases. This is in agreement with Goodman et al., (38) in Nigeria and Alfouwais et al., (39) in Saudi Arabia. In contrast to the study results, Al-Joborae, (32) in Iraq and Al Arrayed et al., (34) reported that the mothers had a fairly good level of awareness of G6PD deficiency. The study results showed some improvement in level of knowledge in comparison with Allahaony et al (40) who reported that only 18.9% of mothers had good knowledge, 48.0% had good attitude and only 25.3% had a good practice towards NNJ and that reflects the effect of health education carried out to the mothers at their study but it shows also that we are still in a bad need to more extensive and focused health education. The results showed that risk factors for hyperbilirubinemia were prematurity, ABO incompatibility, and infection, which is in agreement with (Sadat et al., (41) and Rabiyeepoor, (42) in Iran.

Strengths: The study collectively assessed the prevalence and risk factors of G6PD deficiency besides assessing the level of knowledge, attitude, and practice (KAP) regarding both of G6PD deficiency and neonatal jaundice (NNJ). The study clarified the extent of change towards NNJ based on previous levels published in some research articles in the same region and also drew how much G6PD deficiency despite being a serious disease; it is a poorly known one, making a special recommendation of health education sessions for every mother to be conducted in health centers from day one. A suitable sample size had been studied in a short period, which allowed us to reach large number of mothers and families.

Limitations: There was a need to carry out more investigations to the mothers like direct Coombs test. A posttest to assess the extent of understanding and KAP among the studied mothers was needed. But it was difficult to collect this studied number one more time. We reached only the mothers who sought medical advice for their neonates. Both diseases need KAP assessment among the general population to ensure taking care of the risk factors, but we tried to help the mothers be messengers to their families specially after conducting a health education session to thank them for participation in the study.

Conclusion: G6PD deficiency seems to be an important cause of neonatal jaundice. Cord blood for complete blood count, direct Coombs' test, blood grouping, bilirubin and G6PD screening is

better to be performed in high-risk populations, to early consider a prolonged hospital stay. G6PD deficiency and NNJ are serious conditions so by studying KAP of mothers, the study revealed that mothers' KAP about NNJ despite being still low but it shows promising improvement while KAP about G6PD deficiency is so poor. So it so evitable to apply a mass health education program about both of G6PD deficiency and NNJ to ensure better early detection, good timing treatment and better prevention of the triggering factors to ensure better health of the children.

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Ethical Approval: Institutional Review Boards (IRB) of the Menoufia faculty of medicine had approved the study. Research work had been performed in accordance with the Declaration of Helsinki. A written patient's Consent was taken after explanation of all aspects of the study and gave them the right to withdraw at any time.

Data sharing statement: Data are available to be shared on request by e. mailing zeinabkasemy@yahoo.com

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Legend of figure:

Fig 1: Prevalence of G6PD deficiency among the studied jaundiced neonate group

Fig 2: Total bilirubin distribution among patients with G6PD deficiency, RH incompatibility and ABO incompatibility

Fig 3: Perception of G6PD deficiency and neonatal jaundice among the studied mothers

Table 1: General characteristics of the studied mothers and jaundiced neonates:

General characteristics	Study group (n=487)	
Mothers' characteristics		
Age (Y) (Mean ±SD, range)	31.45±4.77	39-22
Gestational age(week)		
Mean ±SD, range)	37.71±1.05	41-37
Median, IQR	37	37-38
BMI(kg/m2) (Mean ±SD, range)	22.02 ±2.37	27.10-18.30
Gravidity no,%		
≤3	292	60.0
>3	195	40.0
Parity no,%		
≤2	252	51.7
>2	235	48.3
Neonatal characteristics		
Sex: no,%		
Male	339	69.6
Female	148	30.4
Birth weight (kg) (Mean ±SD, range)	2.60±0.29	3.50-2.30
Age of neonate(days) (Mean ±SD, range)	4.45 ±0.86	8-3
Bilirubin(mg/dl) (Mean ±SD, range)		
• Total	15.17 ±5.14	25.50-7.30
• Direct	1.08±0.38	1.50-0.50
• Indirect	13.17 ±3.74	23.15-6.40
Hb (gm/dl) (Mean ±SD, range)	12.18 ±1.75	14.50-9.50
Reticulocyte count (%)(Mean ±SD, range)	3.38 ±1.30	6.0-1.40
Age of onset of jaundice (Maternal recall) (Mean ±SD, range)	3.45±0.85	7-2
Need for Phototherapy on admission (no, %)		
G6PD deficiency	5	0.20
All causes	23	4.7
Family history of G6PD deficiency (no, %)	144	29.6
Consanguinity (no, %)	103	21.1
ABO incompatibility (no, %)	63	12.9
Rh incompatibility (no, %)	47	9.7

Table 2: Distribution of the studied G6PD groups regarding bilirubin, neonate sex, family history and consanguinity:

	G6PD						
	Deficient No.=49 Mean ±SD		Normal No. =438 Mean ±SD		Test of sig	P value	OR CI 95%
Bilirubin(mg/dl)							
• **Total**	23.0 3±2.94		14.30 ±4.55		**t=18.40**	**<0.001***	**-**
• **Direct**	1.38 ±0.14		1.02 ±0.41		**t=12.47**	**<0.001***	
• **Indirect**	17.02 ±3.45		12.74 ±3.52		**t=8.21**	**<0.001**	
Neonate Sex	no	%	no	%			
Male	42	85.7	297	45.0	**χ^2=10.49**	**0.001***	**4.27(1.66-10.99)**
Female	7	14.3	141	55.0			**1.0**
Family history of G6PD deficiency							
+ve	37	75.5	107	24.4	**χ^2=55.21**	**<0.001***	**9.54(4.80-18.95)**
-ve	12	24.5	331	75.6			**1.0**
Consanguinity							
+ve	33	67.3	70	16.0	**χ^2=69.72**	**<0.001***	**10.21(5.39-19.33)**
-ve	16	32.7	368	84.0			**1.0**

***Significant, family history: not in the current family but in their relatives**

Table 3: Knowledge, attitude and practice of the studied mothers regarding G6PD deficiency:

Knowledge	No.=487 no	%
Hearing about G6PD deficiency (per say)		
- Yes	2	4.1
- No	485	95.9
Hearing about fava bean anemia (G6PD Deficiency)		
• Yes	112	23.0
• No	375	76.0
G6PD deficiency is a blood disease		
- Yes	100	89.3
- No	12	10.7
- I don't know	0	0.0
Is it a hereditary disease:		
• Yes	105	93.8
• No	5	4.5
• I don't know	2	1.8
Parents (both or just the mother) have to be carriers for G6PD deficiency to have an affected child?		
- Yes	5	4.9
- No	10	8.9
- I don't know	101	90.2
The inheritance of G6PD deficiency related to the baby's gender?		
- Yes	10	8.9
- No	3	2.7
- I don't know	99	88.4
Knowing whether personally you may have a G6PD deficiency child		
- Yes	8	7.1
- No	85	75.9
- I don't know	29	25.9
There should be a family history of G6PD deficiency to result	75	67.0
- Yes	15	13.4
- No	62	55.4
- I don't know		
Some medications Can trigger an attack of G6PD deficiency	44	39.3
• Yes	10	8.9
• No	58	51.8
• I don't know		
Symptoms of G6PD attack:	10	8.9
Pallor	52	46.4
• Yes	60	53.8
• No		
• I don't know		
Nausea, vomiting, anorexia and diarrhea		
• Yes	15	13.4
• No	45	40.2
• I don't know	52	46.4
Dizziness		
• Yes	30	26.8
• No	5	4.5
• I don't know	77	68.8
Shortness of breath		
• Yes	35	31.3
• No	5	4.5
I don't know	72	66.1
G6PD is a cause of Jaundice		
• Yes	105	93.8
• No	2	1.8
• I don't know	5	4.5

Attitude	no	%
Is this a serious problem		
- Yes	100	89.3
- No	5	4.5
- I don't know	7	6.3
Consanguinity is the cause of the disease		
- Yes	40	35.7
- No	20	17.9
I don't know	52	4.3
Next pregnancy should be prevented:		
- Yes	3	2.7
- No	50	44.6
- I don't know	59	52.7
Follow-up of the diseased child should continue for life	100	89.3
- Yes	2	1.8
- No	10	8.9
- I don't know		

Practice	no	%
Have you been subjected to premarital counseling	112	100.0
- Yes	0	0.0
- No		
Have you been subjected to genetic screening		
- Yes	2	1.8
- No	110	98.2
- I don't know	0	0.0
Seeking medical advice after delivery to be assured	0	0.0
- Yes	112	100.0
- No		

Table 4: Knowledge, attitude and practice of the studied mothers regarding NNJ:

No.=487					
Knowledge	**no**	**%**	**Attitude**	**no**	**%**
Hearing about NNJ			NNJ is a worrisome condition?		
Yes	487	100.0	- Yes	248	50.9
No	0	0.0	- No	200	41.1
Site to detect NNJ			- I don't know	39	8.0
Skin	334	68.6	Phototherapy is the best way in treatment		
Eye	123	25.2	- Yes	409	84
Tongue	30	6.2	- No	8	1.6
Causes			- I don't know	70	14.4
Prematurity	341	70.0	Blood exchange transfusion is the best way of management	107	22
ABO disparity between mother and baby	73	15.0	- Yes	50	10.3
Breastfeeding	146	30.0	- No	330	67.7
Infection	139	33.0	- I don't know		
Hemolysis	194	39.8	Is it important seeking medical advice		
Dehydration	170	34.9	- Yes	450	92.4
Increased U/S examination during pregnancy	292	60.0	- No	20	4.1
Diabetic mothers	73	15.0	- I don't know	18	13.5
Others	141	28.9			
Complications					
Death	146	30.0	**Practice**	**no**	**%**
Cerebral palsy	112	23.0	**Seeking quickly medical advice if having baby with NNJ**		
Mental retardation	170	34.9	- Yes	477	95.9
Handicapping	112	23.0	- No	10	4.1
Hearing loss	30	6.2	- I don't know	0	0.0
			Causes of denial of medical care :	N=10	
Methods of treatment			- Afraid of hospitalization.	6	60.0
Phototherapy	461	94.7	- Admission/ investigation not required.	**1**	10.0
Blood exchange transfusion	146	30.0	- High cost of medical care.	2	20.0
Drugs	399	82.0	- Lack of transportation.	0	0.0
Neon lamp	364	74.7	- Long hours to reach hospital.	0	0.0
Increase breastfeeding	238	48.9	**Time of seeking medical advice**		
			- Within 24-48 h	136	28.5
			- >48 h	341	71.5
			Continuation of breastfeeding		
			- Yes	448	92.0
			- No	39	8.0

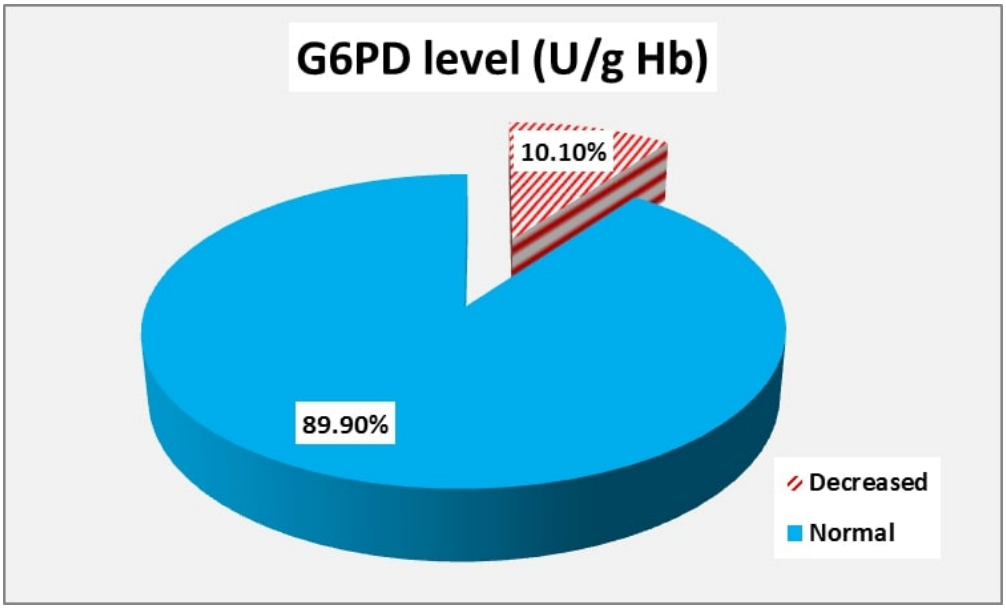

Fig 1: Prevalence of G6PD deficiency among the studied jaundiced neonate group

63x38mm (300 x 300 DPI)

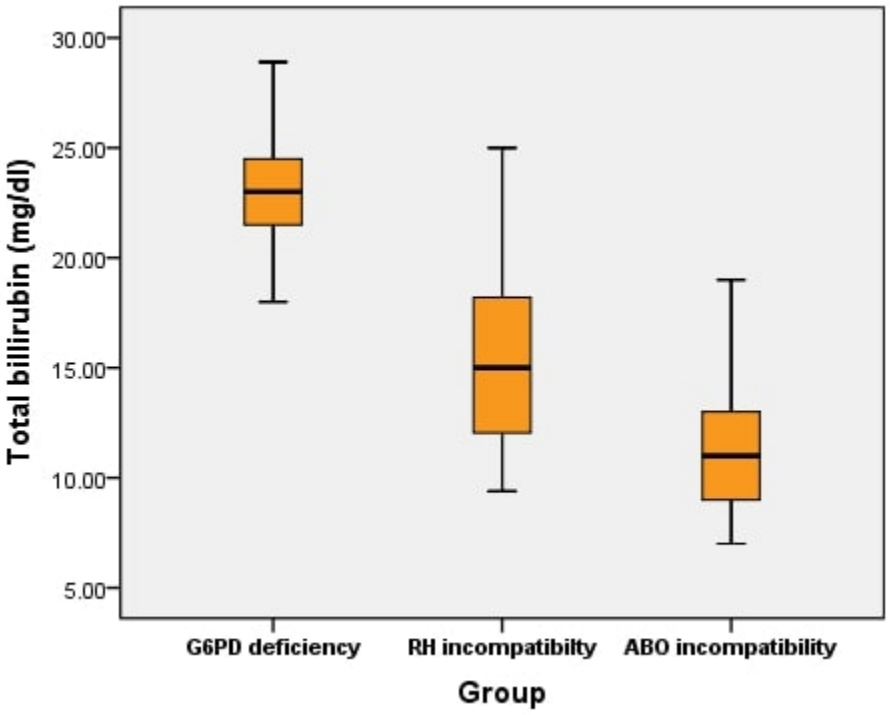

Fig 2: Total bilirubin distribution among patients with G6PD deficiency, RH incompatibility and ABO incompatibility

38x31mm (300 x 300 DPI)

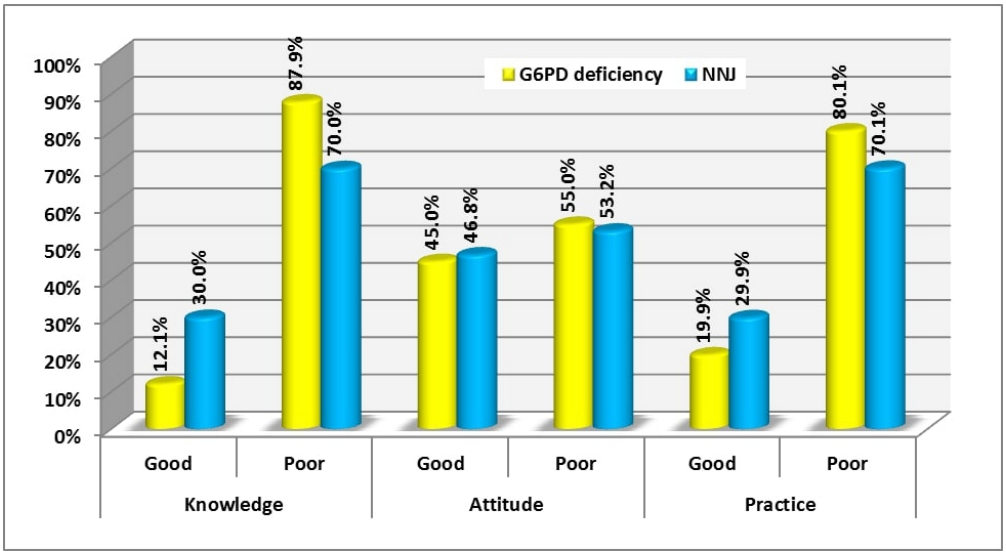

Fig 3: Knowledge, attitude and practice of G6PD deficiency and neonatal jaundice among the studied mothers

82x45mm (300 x 300 DPI)

Questionnaire for assessing Prevalence and Mothers' perception of G6PD Deficiency among Jaundiced Neonates

Mothers' characteristics			
Age (Y):	**Gestational age(week):**	**Wight (Kg):**	**Height** (cm):
Gravidity:	**Parity:**		

Neonatal characteristics		
Sex: Male Female		
Birth weight (kg):	**Age of neonate(days):**	**Age of onset of jaundice:**
Need for Phototherapy on admission	**+ve**	**-ve**
For G6PD deficient cases	+ve	-ve
All patients	**+ve**	**-ve**
Family history of G6PD deficiency	**+ve**	**-ve**
Consanguinity	**+ve**	**-ve**

Lab investigation:	
Bilirubin(mg/dl) • Total • Direct • Indirect	• Hb (gm/dl) • Reticulocyte count • ABO incompatibility • Rh incompatibility
G6PD(u/g Hb):	

Knowledge, attitude and practice of the studied mothers regarding G6PD deficiency:

- **Have you heard about G6PD deficiency (Per say)?**
  -Yes
  -No
- **Have you heard about fava bean anemia (G6PD deficiency)?**
  -Yes
  -No
- **Is fava bean anemia (G6PD deficiency) a blood disease?**
  -Yes **(T)**
  -No
  -I don't know
- **Is fava bean anemia (G6PD deficiency) a hereditary disease:**
  -Yes **(T)**
  -No
  -I don't know
- **Do parents (both or just the mother) have to be carriers for fava bean anemia (G6PD deficiency) to get an affected child?**
  -Yes **(T)**
  -No
  -I don't know
- **Is the inheritance of G6PD deficiency related to the baby's gender?**
  - -Yes (T)
  -No
  -I don't know
- **Do you know whether personally you may have a fava bean anemia (G6PD deficiency) child if you have risk factors?**
  - Yes **(T)**
  - No
  - I don't know
- **Is the family history of fava bean anemia (G6PD deficiency) a condition for occurrence of G6PD deficiency?**
  - -Yes (T)
  -No
  -I don't know
- **Can some medications trigger an attack of fava bean anemia (G6PD deficiency)?**

- -Yes (T)
  -No
  -I don't know
- **Is pallor a symptom of fava bean anemia (G6PD deficiency) attack?**
- -Yes (T)
  -No
  -I don't know
- **May nausea, vomiting, anorexia and diarrhea be symptoms of fava bean anemia (G6PD deficiency) attack?**
  -Yes
  -No **(T)**
  -I don't know
- **May dizziness be a symptom of fava bean anemia (G6PD deficiency) attack?**
- Yes (T)
- No
- I don't know
- **May shortness of breath be a symptom of fava bean anemia (G6PD deficiency) attack?**
- Yes (T)
- No
- I don't know
- **Is fava bean anemia (G6PD deficiency) a cause of Jaundice?**
  - Yes **(T)**
  - No
  - I don't know

Attitude

- **Is fava bean anemia (G6PD deficiency) a serious problem?**
- Yes (T)
- No
- I don't know
- **Is consanguinity a cause of the disease?**
- Yes (T)
- No
- I don't know
- **Should next pregnancy be prevented if there is one child has the disease within the family?**
- Yes
- No (T)
- I don't know
  - **Should follow-up of the diseased child continue for life?**
- Yes (T)
- No
- I don't know

Practice

- **Have you been subjected to premarital counseling?** - Yes -No
- **Have you been subjected to genetic screening?**
- Yes
- No
- I don't know
- **Do you seek medical advice after delivery to be assured?**
- Yes
- No

Knowledge, attitude and practice of the studied mothers regarding NNJ:

- **Have you heard about neonatal jaundice?** - Yes -No
- **What are sites to detect neonatal jaundice**?
- Skin (T)
- Eye (T)
- Tongue (F)

- **What are causes of neonatal jaundice**?
- Prematurity (T)
- ABO disparity between mother and baby (T)
- Lack of breastfeeding (T)
- Infection (T)
- Hemolysis (T)
- Dehydration (F)
- Increased U/S examination during pregnancy (F)
- Diabetic mothers (F)
- **What are complications of neonatal jaundice**?
- Death (T)
- Cerebral palsy (F)
- Mental retardation (F)
- Handicapping (F)
- Hearing loss (F)
- **What are methods of treatment of neonatal jaundice**?
- Phototherapy (T)
- Blood exchange transfusion (T)
- Drugs (F)
- Neon lamp(T)
- Increase breastfeeding(T)

Attitude

- **Is neonatal jaundice a worrisome condition?**
- Yes **(T)**
- No
- I don't know
- **Is phototherapy the best way in treatment?**
- Yes
- No **(T)**
- I don't know
- **Is blood exchange transfusion the best way of management?**
- Yes
- No **(T)**
- I don't know
- **Is it important seeking medical advice?**
- Yes **(T)**
- No
- I don't know

Practice

- **Do you seek medical advice if having baby with NNJ**
- Yes
- No
- I don't know
- **If no why?**
- Afraid of hospitalization.
- Admission/ investigation not required.
- High cost of medical care.
- Lack of transportation.
- Long hours to reach hospital**.**
- **When do you seek a medical advice?**
- Within 24-48 h **(T)**
- >48h
- **Will you continue breastfeeding?**
- Yes **(T)**
- No

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any pre-specified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	3
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	4
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4-5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*4-5*
Bias	9	Describe any efforts to address potential sources of bias	10
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5
		(*b*) Describe any methods used to examine subgroups and interactions	5
		(*c*) Explain how missing data were addressed	-
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	-

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	5-6
		(b) Indicate number of participants with missing data for each variable of interest	-
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	-
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	-
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	-
		Cross-sectional study—Report numbers of outcome events or summary measures	-
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	-
		(*b*) Report category boundaries when continuous variables were categorized	-
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	7
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	-
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	7-8-9
Generalisability	21	Discuss the generalisability (external validity) of the study results	9-10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.
Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.