**Original paper**

# Assessment of the Role of Gender in the Expression of UGT1A1 Gene in Hyperbilirubinemic Neonates

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## Abstract

**Background:** Neonatal jaundice (NJ) is a significant disease among neonates in Najaf province. It manifests 19% of the total deliveries and 50% of the in-patients, and affects about 60% of term and 80% of preterm neonates during the first week of life. UGT1A1 is a cause of concern in NJ, because it is the most important underlying cause of unconjugated hyperbilirubinemia.
**Methods:** A cohort of 85neonate sorted into three groups according to the TSB level. Group 1 (TSB<5mg/dl), group 2 (TSB 5-15 mg/dl) and group 3 (TSB <15mg/l). UGT1A1expression and TSB level was assessed for both males and females in each group.
**Results & Discussion:** Results showed high inverse correlation between UGT1A1expression and the ratio of males (r= -0.99, P<0.01), while females ratio expressed high direct correlation with UGT1A1 expression level with correlation coefficient of (r=0.99, P<0.01).
This might due to physiological maturity differences of liver between both sexes, and the plasma growth hormone (GH) pulses frequencies (released by the pituitary gland) which affects the expression of liver enzymes. It's found that GH pulses are higher in females than in males.
**Conclusion:** concluding that mean UGT1A1 expression level in females is more than that in the males during neonatal period therefore females are less vulnerable to NJ than males.
**Aim:** The aim of this study is to qualify the UGT1A1 gene expression in both males and females therefore determining health and health care requirements.
**Keywords:** Rule of gender in hyperbilirubinemia, Hyperbilirubinemia, Neonatal jaundice, UGT1A1 gene expression.

## Introduction

Neonatal hyperbilirubinemic (NH) can be clinically defined as a yellowish discoloration of the patient's (Neonate's) sclera, skin and soft tissue as a result of bilirubin deposition [(1)], It is first appears in the face and as the bilirubin level rises, it proceeds caudal to the trunk and then to the extremities which makes it appear on nail tips [(2-4)].Neonatal jaundice (NJ) is a significant disease among neonates in Najaf province. According to Az-zahraa teaching hospital for pediatrics and obstetrics (ATHPO) 2012 records, Neonatal jaundice manifests 19% of the total deliveries and 50% of the in-patients. Internationally, NJ affect about 60% of term and 80% of preterm neonates during the first week of life [(5-7)]. Neonatal jaundice is a cause of con-

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cern for both parents and pediatricians [8], because it is a threatening disease for the neonatal mental health and life, since its main complication is kernicterus (encephalopathy)[9-13]., Furthermore prevention of kernicterus is a time and money consuming process, It's found that prevention of one case of kernicterus in USA costing about (5.7) million dollars [14,15], while in Ontario prevention one kernicterus case costing about (0.57) million dollars [16]. Unconjugated bilirubin is the prevalent in the neonatal hyperbilirubinemia[17], this due to defect in either of the four mechanisms involved in blilrubin metabolism (bilirubin uptake, glucuronidation, excretion and entero-hepatic circulation), this defect either physiological which is mild and short term due to immaturity of neonate liver [18] or pathological which is more sever, caused by either infection[19] or genetic alterations in the UGT1A1 enzyme which represent the key element in the conjugation process[20,21], or in the ligandins and membrane bound proteins of the hepatocytes membranes of the cell and organelle that responsible for bilirubin uptake[22-24].

Uridin diphosphate glucuronosyle transferase 1A1 ( UGT1A1) is a cause of concern in NJ, because it is the most important underlying cause of unconjugated hyperbilirubinemia[25] not only in neonatal period but along with the course of life. Impairment of UGT1A1leades to impairment in detoxification of vast number of aromatic compounds including bilirubin, steroids( including steroid hormones) and some drugs such as irinotecan which is used as anti-cancer drug[26-28]. Data from Azzahraa Teaching Hospital for Obstetrics and Pediatrics revealed that NJ was more incident in males than females. UGT1A1 expression was examined to assess the the rule of gender in UGT1A1 expression, thereby aiding in individual and family disease management [29-31].

## Methods

The present study was performed during the period from May to November 2013 in Az-zahraa Teaching Hospital for Pediatrics and Obstetrics and Annajaf Private Clinical Laboratory. The chemicals that used in this study listed in (tab. 1), whereas the apparatus and equipments used listed in (tab. 2).

Table 1.chemicals used in this study.

| No. | Chemicals | Source |
|---|---|---|
| 4 | Grade water. | Parental- India |
| 5 | Human UGT1A1 ELISA kit | Cusabio- China |

Table 2. Apparatus and Equipment used in this study.

| No. | Equipment | Source |
|---|---|---|
| 1 | Centrifuge | Kokusan-19F Japan |
| 2 | ELISA reader | Bio-rad |
| 3 | Micropipette filtered tips. | Bioneer- Korea |
| 4 | Micropipette set (0.1-1000µl) | Biobasic- Canada |
| 5 | Multichannel micropipette | Ependrof |
| 6 | Timer alarm | China |
| 7 | U.V.-spectrophotometer | APEL- Japan |
| 8 | Incubator | Memmert- Germany |
| 9 | Refrigerator | Arjelic- Turkey |

A cohort of 85neonate subjects were used in this study, these cohorts sorted into three groups according to the TSB level. Group 1 represent the subjects whom TSB level was less than 5mg/dl, group 2 represent the subjects whom TSB level was from 5-15 mg/dl and group 3 represent the subjects whom TSB level was more than 15mg/l. UGT1A1expression and TSB level was assessed for both males and females in each group.

A sample of 1ml venous blood was collected from these subjects, transferred to golden capped serum separating tubes (SST), left to clot for sufficient time, centrifuged at 3000 rpm for 15 min. Serum aliquot and stored in -24C$^{o}$ to the time the ELISA test where performed. TSB examined directly for the fresh sera. Reagents, standards and sera prepared for UGT1A1 assessment. UGT1A1level assessed according to the manufacturer's protocol, optical density (OD) measured using ELISA reader and standard curve between OD and concentration; then drawn.

Curve expert software version (1.4) used to determine the standard curve fit and calculate the UGT1A1 concentration from analogous OD for each sample.

# Results

Among groups statistics using student's t-test and correlation revealed that there is a high correlation between gender and UGT1A1 expression. The present study showed high inverse correlation between UGT1A1expression and the ratio of males (r= -0.99, P<0.01) (fig.1), while females ratio expressed high direct correlation with UGT1A1 expression level with correlation coefficient of (r=0.99, P<0.01) (fig. 2).

## Discussion

Data analysis showed that mean UGT1A1 expression level in females is more than that in the males during neonatal period (tab. 3); so it is in accord with the results of [32],[33]. Therefore females are less vulnerable to severe NH than males.Liver-expressed genes are differing in males and females. Expression of these genes is affected by the profile of plasma growth hormone (GH) released by the pituitary gland in pulsatile form. The frequencies of GH pulses are higher in females than in males [34].

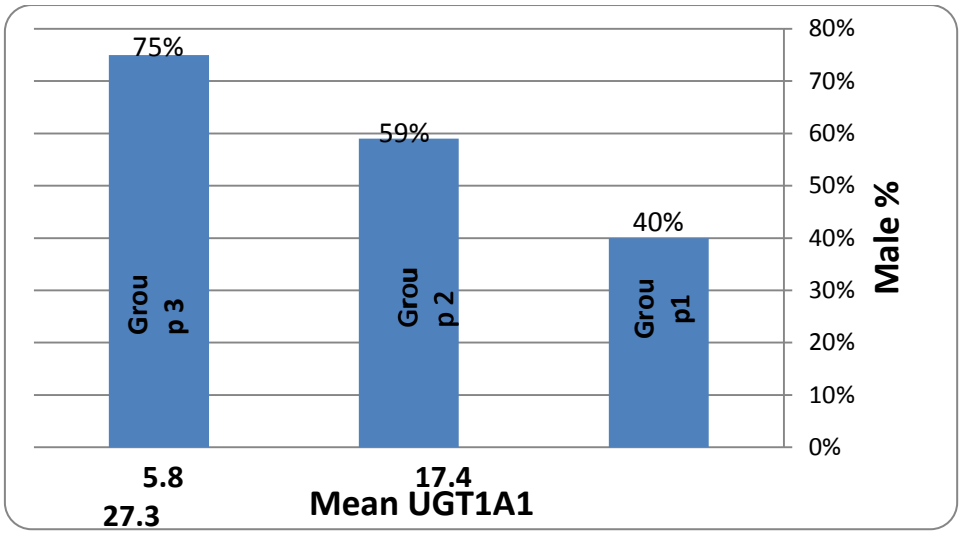


Figure 1.UGT1A1expression in male jaundiced neonates in the three groups.

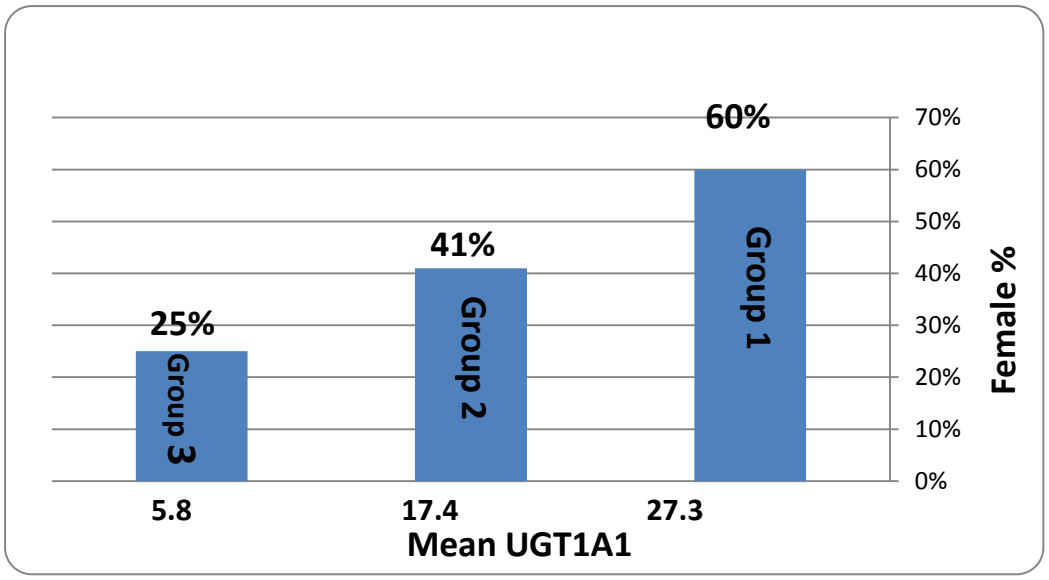


Figure 2.UGT1A1expression in female jaundiced neonates in the three groups.

Table 3. Relationship between gender and both UGT1A1 expression and TSB level, N=85.

| Parameters | r ± SE | P-value |
|---|---|---|
| UGT1A1, M% | -0.99 ± 0.023 | P<0.01 |
| UGT1A1, F% | 0.99 ± 0.023 | P<0.01 |

## Conclusion

Data analysis showed that mean UGT1A1 expression level in females is more than that in the males during neonatal period (tab. 1); therefore, females are less vulnerable to severe NH than males.

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