

Effect of fetal sex and seasonal variation on the level of neonatal hyperbilirubinemia

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ABSTRACT

Introduction: Yellowish discoloration of sclera and skin in the neonatal period known as Neonatal jaundice as result of increased level of bilirubin in the blood, the bilirubin is formed when the red blood corpuscles break down by any reason and the immature liver cannot remove it from the circulations, if the destruction of red blood cells is much more than the rate of liver clearance the high level of bilirubin and neonatal jaundice appear, sex and gender affect the level of bilirubin during the neonatal period illness and the bilirubin level changed according to seasonal variation. **Objectives:** The aim of the study was to know the variation of neonatal bilirubin level with the variation of season and variation of sex of the patients. **Design:** Our study was done in Zagazig general hospital in the Obstetrics department and PNICU Unit in the period from October 2013 to August 2014, the number of patients equal in summer and winter also equal in sex. **Methods:** The study was done over 500 newborns with jaundice clinically diagnosed and they divided to equal group with same sex and in same season, we measured the total, direct and indirect level of serum bilirubin for all neonates enrolled in the study. **Results:** Our study recorded 1575 deliveries 838 cases delivered during summer season and 737 delivered during winter season out of them 420 delivered by caesarean section during summer season C.S. during summer 220 cases and 200 delivered in winter season out of them 13 patients were assisted 7 during summer and 6 during winter. They divided equally to 250 male and 250 female also 250 baby in summer and 250 during winter we found the higher level of unconjugated bilirubin is high especially in summer season in males while conjugated bilirubin were in females in winter season. Increased unconjugated bilirubin in males more common in males born in summer than males born in winters $P=0.41$. While conjugated bilirubin raised more common in females compared to males $P=0.20$. Total and unconjugated bilirubin between females neonates were significantly raised during delivered in summer $P=<0.001$, $P=<0.001$ while conjugated was raised in neonates born during winters $P=0.003$. **Conclusion:** During the summer season high increased temperature influence higher effect of breast feeding lead to increased bilirubin level. Means that hyperbilirubinaemia occurred in summer season and in males neonates.

Key words: Neonatal jaundice, gender& neonatal hyperbilirubinemia, seasonal hyperbilirubinemia.

Introduction

Neonatal jaundice as result of increased level of bilirubin in the blood, the bilirubin is formed when the red blood corpuscles break down by any reason and the immature liver cannot remove it from the circulations, if the destruction of red blood cells is much more than the rate of liver clearance the high level of bilirubin and neonatal jaundice appear, neonatal hyperbilirubinemia is associated with a variety of conditions. Hyperbilirubinemia appears in approximately 60% of the newborns at term and almost in all preterm neonates, with prevalence more than 85%. (Lancet of detection and treatment of neonatal hyperbilirubinemia, 2010; Seidman, *et al.*, 2011) most newborns, jaundice is a benign condition. Less efficient hepatic conjugation, and enhanced bilirubin absorption by the enterohepatic circulation. (Voeng and Chiu, 2010) In addition to physiologic jaundice, common identified pathologic causes include isoimmune hemolytic disease and glucose-6-phosphatase dehydrogenase (G6PD) deficiency. (Voeng and Chiu, 2009; Ahn *et al.*, 2000; Green *et al.*, 2013) Several studies have revealed that in the absence of any jaundice, a total serum bilirubin (TSB) level of 12 mg/dL is extremely unlikely. (Vatchkio, 2005; Pheutani and Johnson, 2006) Although a

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safe threshold for TSB has not been defined, most physicians have adopted a TSB ≥ 20 mg/dL as indicating vulnerability to kernicterus and neurotoxicity. (Nic., 2012) Many environmental factors influence neonatal hyperbilirubinemia. Etiologies leading to NH can carry a geographic difference as for instance, in one study, NH was shown to be more common in babies of Chinese ethnic origin than those of Indian, Malay and other origins. (Aly *et al.*, 2005) In uterine conditions have also been shown to influence neonatal hyperbilirubinemia. There are many different conditions that can cause elevated unconjugated bilirubin in newborns. These include hemolysis, syphilis, haemorrhage and a number of other conditions. Unconjugated bilirubin in newborns tends to be higher than the normal value for adults. The placenta is responsible for removing unconjugated bilirubin. In most cases, the normal functioning of baby's liver system will ensure that this difference in the value of bilirubin corrects itself over time. Direct (Conjugated) bilirubin in newborns is also processed through the liver and bile system of the infant. A failure of any of these systems due to development problems will lead to increased level of Conjugated (direct) bilirubin. (Mofid *et al.*, 2013) In some cases, the baby's position affects the level of bilirubin in newborns. There have been cases where an entanglement of the umbilical cord has led to the development of high levels of indirect (unconjugated) bilirubin in newborns. (Mofid *et al.*, 2013) Gender & sex influence on neonatal illnesses and outcomes. Many clinically observable differences influencing neonatal hyperbilirubinemia have been reported to be subject to gender bias in the newborn: Apgar scores, pulmonary disease (respiratory distress syndrome), intravascular hemorrhage (IVH), and urinary tract infection, (Sirvant Mayor *et al.*, 1996) but there is no consensus data regarding influence of gender (sex) on neonatal hyperbilirubinemia. Empirical neonatological experience suggests that prevalence and degree of neonatal jaundice might be dependent on seasonal variation also, mainly due to the sunshine duration. (Dolas *et al.*, 2013) The higher temperature during the summer have also shown to contribute to the qualitative and quantitative differences found in bilirubin in this season, with a greater influence of breastfeeding and more severe hyperbilirubinemia. However, evidence-based data on this issue are scarce. (Tanig *et al.*, 2004) The purpose of this study is to identify the differences in neonatal hyperbilirubinemia according to fetal sex (gender) and seasonal variation (hot, cold).

Materials and Methods

Our study was done in Zagazig general hospital in the Obstetrics department and PNICU Unit in the period from October 2013 to August 2014, the number of patients equal in summer and winter also equal in sex.

Methods:

The study was done over 500 newborns with jaundice clinically diagnosed and they divided to equal group with same sex and in same season, we measured the total, direct and indirect level of serum bilirubin for all neonates enrolled in the study 250 of both sex diagnosed clinically divided equally in summer and winter season were taken. Eligible infants enrolled had an estimated gestational age of 37 weeks, who survived >2 days had no major anomalies, and had parental consent for study participation. Color of skin shown by inspection was used to detect newborn with neonatal jaundice then followed by laboratory investigations to measure total, conjugated and unconjugated bilirubin level in blood also coombs test, reticulocytic count and RH factors all were made in the second day of live in cases with jaundice (Glouria Bottini *et al.*, 2000). Out come of labor 35 w gestational age with metabolic diseases in the form of aminoacidopathy affecting the basal ganglia, neurofibromatosis, acidosis with hypoxia, hypothermia ,asphyxia, meningitis and septicemia were excluded from our study because these conditions lead to decreased albumin binding, low serum albumin level, binding interference by drugs, also excluded sever congenital anomalies, syndromic malformations, chromosomal deformity, (toxoplasmosis, rubella, cytomegalovirus, herpes and syphilis)and immunodeficiency diseases were excluded.

Results

Our study recorded 1575 deliveries 838 cases delivered during summer season and 737 delivered during winter season out of them 420 delivered by caesarean section during summer season C.S. during summer 220 cases and 200 delivered in winter season out of them 13 patients were assisted 7 during summer and 6 during winter. They divided equally to 250 male and 250 female also 250 baby in summer and 250 during winter we found the higher level of unconjugated bilirubin is high especially in summer season in males while conjugated bilirubin were in females in winter season. Increased unconjugated bilirubin in males more common in males born in summer than males born in winters $P=0.041$. While conjugated bilirubin raised more common in females compared to males $P=0.20$. Total and unconjugated bilirubin between females neonates were significantly raised during delivered in summer $P<0.001$, $P<0.001$ while conjugated was raised in neonates born during winters $P=0.003$. Mean total, direct and indirect serum bilirubin level of newborns born in winters was 11.33 ± 2.83 mg/dl, 0.63 ± 0.39 mg/dl and 10.70 ± 2.44 mg/dl, respectively, while in those born in summers was 12.42 ± 4.68 mg/dl, 0.61 ± 0.45 mg/dl and 12.07 ± 4.58 mg/dl respectively. Thus total and indirect bilirubin was higher in newborns born in summers as compared to those born in winters ($P < 0.001$).

Table 1: Discus seasonal variation and neonatal hyperbilirubinemia

| Level of bilirubin | Winter season | Summer season | P |
|--------------------|------------------------|------------------------|----------|
| Total bilirubin | 11.33 ± 2.83 mg/dl | 12.42 ± 4.68 mg/dl | <0.001 |
| Conjugated | 0.63 ± 0.39 mg/dl | 0.61 ± 0.45 mg/dl | >0.05 |
| Unconjugated | 0.61 ± 0.45 mg/dl | 12.07 ± 4.58 mg/dl | <0.001 |

Table 2 shown the values of mean, total and indirect bilirubin was slightly higher in males 12.29 ± 4.37 mg/dl and 11.67 ± 4.23 mg/dl, respectively as compared to females 11.76 ± 3.39 mg/dl and 11.09 ± 3.43 mg/dl, respectively but mean direct bilirubin was slightly higher in females 0.61 ± 0.37 mg/dl in comparison to males 0.63 ± 0.49 mg/dl, though these differences were not statistically significant.

Table 2: Discus Variation in neonatal hyperbilirubinemia and gender

| Level of bilirubin | Male sex | Female sex | P |
|--------------------|------------------------|-------------------------|---------|
| Total bilirubin | 12.29 ± 4.37 mg/dl | 11.76 ± 3.39 mg/dl | >0.05 |
| Conjugated | 0.63 ± 0.49 mg/dl | 0.61 ± 0.37 mg/dl | >0.05 |
| Unconjugated | 11.67 ± 4.23 mg/dl | 11.09 ± 3.43 mg/dl, | >0.05 |

This table 2 demonstrates the difference in NH according to gender. Thus taking both seasonal and gender variations together, serum bilirubin was higher in males in summers and mainly comprised of unconjugated bilirubin while direct bilirubin was higher in females in winters.

Table 3 shown mean direct bilirubin in females during winter was 0.67 ± 0.45 mg/dl and in males was 0.57 ± 0.28 mg/dl only. This value suggests that direct bilirubin was more common in females as compared to males and was found to be statistically significant $P = .019$. While indirect and total bilirubin level in males were 10.97 ± 3.07 mg/dl and 11.49 ± 3.16 mg/dl respectively, while in females indirect and total bilirubin level were found to be 10.46 ± 2.55 mg/dl and 11.10 ± 2.52 mg/dl, respectively. Although these values were higher in males as compared to females, they were not statistically significant

Table 3: demonstrates these seasonal variations in NH in male and female neonate

| Level of bilirubin | Winters | | summers | |
|--------------------|------------------------|------------------------|------------------------|------------------------|
| | Males | Females | Males | Females |
| Total bilirubin | 11.49 ± 3.16 mg/dl | 11.10 ± 2.52 mg/dl | 13.12 ± 5.30 mg/dl | 12.41 ± 4.12 mg/dl |
| Conjugated | 0.57 ± 0.28 mg/dl | 0.67 ± 0.45 mg/dl | 0.62 ± 0.62 mg/dl | 0.55 ± 0.19 mg/dl |
| Unconjugated | 10.97 ± 3.07 mg/dl | 10.46 ± 2.55 mg/dl | 12.41 ± 5.16 mg/dl | 11.13 ± 4.12 mg/dl |

Table 3 : During summer total, direct and indirect bilirubin in males was 13.12 ± 5.30 mg/dl, 0.62 ± 0.62 mg/dl and 12.41 ± 5.16 mg/dl, respectively. In females total, direct and indirect bilirubin

was 12.41 ± 4.12 mg/dl, 0.55 ± 0.19 mg/dl and 11.13 ± 4.12 mg/dl. So hyperbilirubinemia is more in males compared to females during summer.

Discussion

Neonatal jaundice as result of increased level of bilirubin in the blood, the bilirubin is formed when the red blood corpuscles break down by any reason and the immature liver cannot remove it from the circulations, if the destruction of red blood cells is much more than the rate of liver clearance the high level of bilirubin and neonatal jaundice appear, neonatal hyperbilirubinemia is associated with a variety of conditions. Hyperbilirubinemia appears in approximately 60% of the newborns at term and almost in all preterm neonates, with prevalence more than 85%. Most newborns, jaundice is a benign condition (Lancet of detection and treatment of neonatal hyperbilirubinemia, 2010; Seidman *et al.*, 2011). Less efficient hepatic conjugation, and enhanced bilirubin absorption by the enterohepatic circulation. There are Different reasons causing hyperbilirubinemia in the neonatal period they are varying according to the season and the sex of the baby as recorded by (Buckley and Klaassen, 2009), in our study direct bilirubin is more common in females born in winters as compared to males born in winters ($P = 0.020$) and to females born in summers ($P = 0.003$). The rise of serum bilirubin in winters is higher, can possibly due to less sunshine duration, (Dolas *et al.*, 2013) and due to the fact that children born in the winter period are more exposed to other contributing agents, such as infections leading to inflammation of the liver-biliary system and obstructive jaundice, thus increasing direct bilirubin. The reason of more incidence of direct bilirubin in females is unknown and beyond the scope of our study. Our study recorded 1575 deliveries 838 cases delivered during summer season and 737 delivered during winter season out of them 420 delivered by caesarean section during summer season C.S. during summer 220 cases and 200 delivered in winter season out of them 13 patients were assisted 7 during summer and 6 during winter. They divided equally to 250 male and 250 female also 250 baby in summer and 250 during winter we found the higher level of unconjugated bilirubin is high especially in summer season in males while conjugated bilirubin were in females in winter season. Increased unconjugated bilirubin in males more common in males born in summer than males born in winters $P=0.41$. While conjugated bilirubin raised more common in females compared to males $P=0.20$. Total and unconjugated bilirubin between females neonates were significantly raised during delivered in summer $P=<0.001$, $P=<0.001$ while conjugated was raised in neonates born during winters $P=0.003$. Some (Dollberg *et al.*, 1990; Baytur *et al.*, 2004) other studies lower bilirubin levels after Cesarean section are reported and are supposedly explained by placental transfusion or timing of cord clamping. In our study total and indirect bilirubin was higher in newborns born in summers as compared to those born in winters $P < 0.001$; season can act as an independent etiological factor of NH. Indirect bilirubin levels were found to be higher in both male and female neonates born in summer than those born in winter in respective gender $P = 0.041$ for males, <0.001 for females. On the other hand, total bilirubin levels were higher only in females born in summer as compared to those born in winter $P < 0.001$. Although the value of direct and total bilirubin levels were also found to be higher in males born in summer as compared to those born in winters but this was not significant. The possible reason can be that higher temperature during the summer could contribute to the qualitative and quantitative differences found in NH. (Tanig *et al.*, 2004) Sirvant Mayor *et al.* (1996) also observed more pathologic hyperbilirubinemia during the fall and less (Lancet of detection and treatment of neonatal hyperbilirubinemia, 2010; Seidman *et al.*, 2011) in winter, but in their study, these differences between seasons were not statistically significant. This difference found in summer by them was due to breast milk jaundice. In summers neonates tends to drink more of breast milk and this breast milk inhibits UDP-GT leading to rise in unconjugated bilirubin and more infants with maximum serum bilirubin >20 mg/dl and more admissions from external delivery rooms. (Tanig *et al.*, 2004) Sirvant Mayor *et al.* (1996) proved that high unconjugated bilirubin levels gives protection against oxidative stress. Recent studies also suggest a beneficial action of bilirubin due to its protective effect from secondary oxidants. Since the newborn infant is very sensible to oxidative damage, it is possible that seasonal variation of bilirubin level during the first few days of life may influence further development and susceptibility to pathological manifestations. So rise of serum bilirubin level during the first 24 hours of life has been shown to depend on season of birth (more stress in summers). Glouria *et al.*, (2000) Recording that

hyperbilirubinemia is more in males as compared to females during summer though it was not significantly high. (American Academy of Pediatrics Subcommittee on Hyperbilirubinemia. 2004) Fevery *et al.* (2008) significant association between G-6-PD deficiency and NH was also shown in males in another study but not in female neonates. In this study male neonates had a considerably higher incidence of neonatal jaundice than did female neonates and there was an inverse dose-response in relation between G-6-PD activity and neonatal jaundice among male neonates. Thus, higher bilirubin in the hospitalized male infant may also be a reflection of various maturational and genetically determined pathophysiological characteristics in males which may be physiologically beneficial. Unfortunately, such an effect can only be supported in the future through the analysis of a more comprehensive data set. (Sirvant Mayor *et al.*, 1996) Several other clinical factors like Apgar scores, pulmonary disease (respiratory distress syndrome), IVH, and urinary tract infection have been shown to subject to gender bias in the newborns. These factors also indirectly contribute to hyperbilirubinemia. These are reported more common in males. This male disadvantage or the Y-chromosome effect has been postulated to be responsible for these differences. The role that various gender-biased biologic mechanisms contribute to the observed male disadvantage can only be speculated. Tioseco *et al.* reported high peak serum bilirubin in males with low birth weight (weight, 1500-2499 g) when compared to females, in addition to association with other risk variables such as sepsis and IVH. The difference in IVH prevalence is worth further analysis and could be attributed to differences in severity of illness in the male group. (Sirvant Mayor *et al.*, 1996) Indirectly it can be understood that, when there is indirect bilirubin in infants, it is highly likely that the infant will suffer from malnourishment (less birth weight). In such a situation, a surgical birth may be prescribed, as the chances of the child surviving a normal birth will be reduced, (Mofid *et al.*, 2013) thus increasing a chance of hyperbilirubinemia as type of the anesthesia used for c/s and delivery mode may also affect the risk for hyperbilirubinemia, (Dollberg *et al.*, 1990; Baytur *et al.*, 2004) as already said. The small difference in bilirubin noted between male and female infants, although statistically significant, may appear clinically trivial. However, the results of this study rekindle the interest in a topic studied in the past, namely the super-female newborn, albeit with a new application. The study has some limitations because it did not correlate peak bilirubin levels with initiation and type of feed, or with the use of phototherapy, and the fact that in the country like India care-givers may be influenced by gender in their management of these infants. Moreover, hematocrit levels were not controlled in this study. Also there can be difference in bilirubin by the discrepancy in mortality rates between males and females. More of the sicker males may have died in the first 2 days curtailing their opportunity to demonstrate their peak bilirubin levels.

Conclusion

Serum bilirubin was higher in males in summers and mainly comprised of unconjugated bilirubin while direct bilirubin was higher in females in winters, hyper-bilirubinemia is more in males compared to females during summer.

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