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THE STUDY ON THE EFFECT OF GENDER ON SERUM BILIRUBIN CONCENTRATION IN INFANTS WITH NEONATAL HYPERBILIRUBINEMIA

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ABSTRACT

The study was undertaken to observe the gender based variation in serum bilirubin levels in neonatal Hyperbilirubinemia. A total of seventy nine healthy full term infants (50 females and 29 males) in age group of 1-7 days, who presented with visible non-hemolytic hyperbilirubinemia were analyzed. There was no significant difference in maternal age, gestational age, birth weight and perinatal age in between male and female infants. Total bilirubin levels were high both in female and male infants and there was no significant difference between them. But the direct bilirubin levels were significantly high in female infants compared to male infants during the neonatal period.

KEYWORDS: **Direct bilirubin, hyperbilirubinemia, neonate, serum total bilirubin**

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INTRODUCTION

Hyperbilirubinemia is the most common condition requiring evaluation & treatment in the newborn. The clinical manifestation of hyperbilirubinemia - jaundice occurs in 60% of normal and nearly all preterm infants[1]. An alteration in the equilibrium between bilirubin production, transport and excretion causes a transitional increase during neonatal period[2, 3]. The common risk factors for unconjugated hyperbilirubinemia include fetal-maternal incompatibility, prematurity, low birth weight, previous sibling with history of jaundice, breast feeding, cephalhematoma, trauma from instrumental delivery, delayed meconium etc[4, 5]. Physiological jaundice represents physiological immaturity of the neonates to handle increased bilirubin production.Visible jaundice appears between 24-72 hours of age, peaks at 4 to 5th day in term infants and 7th day in preterm infants and disappears by 10 to 14 days of life. It is predominantly unconjugated bilirubin and levels do not exceed 15mg/dl[6]. The average peak bilirubin concentration of full term newborn infant is 5 to 6 mg/dl and exaggerated physiological jaundice occurs at values above this threshold. Jaundice in breast-fed infants appears between 24-72 hours of age, peaks by 5-15 days of life and disappears by the third week of life[6]. Appearance of jaundice within 24 hours, rapid increase in serum bilirubin level (5mg /day), total serum bilirubin concentrations higher than 17 mg/dl in full term infants and conjugated bilirubin level more than 20% of total serum bilirubin concentration are considered to be pathologic[6, 7]. In the present study, we estimated total bilirubin, direct bilirubin levels in male & female neonates and correlated with the effect of gender on bilirubin levels during neonatal period.

MATERIALS AND METHODS

Neonatal hyperbilirubinemia defined as total serum bilirubin level more than 5 mg/dl (86 µ mol per L) [4]. The study was conducted on seventy nine full term infants, 50 females and 29 males in the age group of 1-7 days, with clinically suspected jaundice in the department of Biochemistry, Bhaskar Medical College, between January 2008 to June2008. Informed consent was obtained from the parents. Full term babies with serum total bilirubin levels more than 5mg/dl were included in the present study. Infants with cephalhematoma, meconium aspiration, Rh incompatibility, conjugated bilirubin more than 2mg/dl and congenital hypothyroidism were excluded. Infants who were born at less than 36 weeks gestational age were also excluded. The clinical & laboratory data were analyzed. The concentrations of serum total bilirubin (STB), direct bilirubin (DB) or conjugated bilirubin were estimated in the centrifuged venous samples of clinically suspected cases of neonatal hyperbilirubinemia. STB & DB were estimated by diazo method using Erba kit on Erba chem.-5 plus instrument. (Serum total bilirubin=unconjugated +conjugated bilirubin).

STATISTICAL ANALYSIS

In statistical analysis, descriptive statistics like mean and standard deviation were calculated for all variables by groups. Mean values of all the variables were compared between groups using student's test. Level of significance was considered as 0.05.

RESULTS

The clinical and laboratory data in each case were analyzed. Out of 210 samples received, in 6 samples conjugated bilirubin levels were more so excluded, 90 met the case definition, 11 had incomplete data,79 were with full data, 50 (63%) were female infants, 29 (37%) were male infants. All the infants were on exclusive breast feeding.

Maternal Parameters

In 55 (70%) of the infants maternal age was between 21-25 years age, 15 (19%) of the infants 18-20 years and in 8 (10%) of the infants

it was between 26-30 years age. The mean maternal age in female infants was 22.68 ± 2.34, in male infants 22.55 ± 2.24, the difference was statistically not significant (p= 0.809). 59 (75%) women were pregnant with their first child. 39 (50%) were vaginal deliveries, 10 (13%) were instrumental deliveries, 29 (37%) were caesarean sections. List of the various fetomaternal parameters considered to be affecting female & male infants and their percentage was shown in (Table 1).

Fetal parameters

A total of 79 infants (50 female & 29 male) were investigated. 57 (73%) infants have birth weight more than 2.5 kg, 21 (27%) infants have birth weight less than 2.5kg. The mean birth weight was 2.74 ± 0.30 in female infants, 2.91 ± 0.43 male infants, the difference being statistically not significant (p = 0.07). The mean gestational age was 37.96 ± 0.69 for female infants, 38.13 ± 0.69 for male infants and there was no significant difference in gestational age in both female & male infants (p=0.27).The mean postnatal age was 3.54± 1.75 in female, 3.34± 1.47 in male infants the difference was statistically not significant (p = 0.58).The mean Total Bilirubin 11.43 ± 3.29 in female infants, 11.52 ± 2.67 in male infants, the difference was statistically not significant (p=0.89). The mean direct bilirubin 1.57 ± 0.32 in female infants, 1.37 ± 0.35 in male infants and the direct bilirubin levels between female & male infants is statistically significant (p=0.01) but the values were less than 2mg/dl.(Table 2).Mean values of total bilirubin & direct bilirubin in female &male infants were shown in graph 1 and their mean, standard deviation and p values are given in the table 2.

Table 1

List of the various fetomaternal parameters considered to be affecting female & male infants and their percentage

Parameter	Female infants (n=50)	Male infants (n=29)	Total (n=79)
Maternal factors			
Age of the mother(years)			
18-20	9	6	15(19)
21-25	35	20	55(70)
26-30	5	3	8(10)
Parity			
P1	36	23	59 (75)
P2	11	6	17(22)
P3	2	0	2(3)
Mode of delivery			
Normal	23	16	39(50)
Outlet	6	4	10(13)
Cesarean section	20	9	29(37)
Fetal factors			
Gestational age			
>37 wks	50	29	79(100)
Breast feeding	50	29	76 (100)
Birth weight			
<2.5	15	6	21(27)
>2.5	34	23	57(73)

Graph 1
Mean values of total bilirubin & direct bilirubin in female & male infants

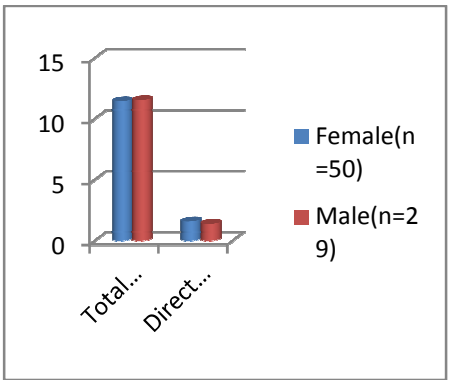

Table 2
MeanSD&P values of the parameters

Parameter	Female(n=50)	Male(n=29)	P Value
Maternal age	22.68 ± 2.34	22.55 ± 2.24	0.809
Gestational age	37.96 ± 0.69	38.13 ± 0.69	0.27
Postnatal age	3.54± 1.75	3.34± 1.47	0.58
Birth weight	2.74 ± 0.30	2.91 ± o.43	0.07
Total Bilirubin	11.43 ± 3.29	11.52 ± 2.67	0.89
Direct Bilirubin	1.57 ± 0.32	1.37 ± 0.35	*0.01

***** P<0.05:* P<0.01***

DISCUSSION

Hyperbilirubinemia is felt to be benign condition for infants born at term or near term gestation. Neonatal hyperbilirubinemia results from an increase in bilirubin load in hepatocytes decreased hepatic uptake and defective conjugation of bilirubin. In some of the previous studies there was an increased incidence in male infants and in some studies there was no difference in bilirubin levels between male &female infants[2]. The male disadvantage or Y chromosomes effect has been postulated to be responsible for this gender based difference in the new born. Dysfunction of the placenta, higher metabolic rate in the male infants etc were also the contributing factors[2].Uridinediphosphate-glucuronyltransferase (UDP-GT) catalyses the addition of glucoronic acid to endo and xeonobiotics increasing hydrophilosity and enhancing elimination[8]. UDP-GT is immature at birth and formation of UDP-GT is encoded by gene UGT1A gene on chromosome 2[9]. Gender divergent glucoronidation rates were observed in humans & rats and gender difference in UDP-GT mRNA levels has been observed in rodents[8]. In a study done by John fevery, the serum levels of unconjugated bilirubin were lower in female during reproductive age than in male, this might be due to oestro-progesteron and testosterone effect on conjugation rate because testosterone down regulates UDP-GT, whereas combination of oestro-progesterone enhances enzyme activity[9]. Hill et al observed high concentrations of estrogens and certain progesterones in the fetal blood and it was also suggested that fetuses exposed to stress during labor produce higher progesterone secretion, which may protect the fetuses against sequelae of hypoxia[10]. Study conducted by Muraca and Fevery revealed that the activity rate of UDP-GT was higher in adult female rats than males rats and in their studies gonadectomy decreased enzyme activity in females and increased it in

male rats suggesting that sex hormones may be an important regulators of bilirubin conjugation[11]. We undertook the present study to observe the gender based variation in serum bilirubin levels during neonatal period. In our study there was no significant difference in maternal age, gestational age, birth weight and perinatal age between female and male infants. The total bilirubin levels were also elevated in both female & male infants during neonatal period in our study. These findings are in accordance with the study conducted by Aliyu Muhammad e al. They reported a significant high mean concentration of bilirubin in jaundiced infants compared to healthy infants during neonatal period[13]. In the present study the difference in total bilirubin between female & male infants was not statistically significant. Similarly observations were correlated from the study by Agarwal et al in which the fetal sex and birth weight were not found to be significantly affecting neonatal hyperbilirubinemia[12]. On the other hand in our study the direct (conjugated) bilirubin levels were significantly high in female infants than male infants and were less than 2mg/dl. This indicates that bilirubin conjugation is better in female infants than male infants and indirectly it also supports the high unconjugated bilirubin levels in male infants during neonatal period. In accordance to this Jennifer A.Tioseco et al reported high peak serum bilirubin in male low birth weight babies and the difference in bilirubin levels were significantly high only in the larger birth weight category (weight, 1500-2499 g) and it was thought that other risk factors such as sepsis and intra vascular hemorrhage etc., may play an important role than gender in influencing bilirubin levels in the smaller-weight categories[2]. High unconjugated bilirubin levels gives protection against oxidative stress[2]. Hyperbilirubinemia can be aggravated by lactation failure, but it also occurs in the presence of successful lactation[14, 15]. It is due to dehydration, caloric deprivation and enhanced enter hepatic circulation[16, 17]. In the present study all the infants who were exclusively on breast feeding and were associated with elevated serum total bilirubin levels. Similar observations were found in the study of Maisels and Gifford et al where serum bilirubin concentration greater than 12.9 mg/dl was strongly associated with breast feeding and percentage of weight loss, decreased gestational age, male sex, bruising and induction of labour[15]. Chang PF and Cheng et al documented that male breastfed neonates with a variant nucleotide 211 in UGT1A1 have a high risk for developing prolonged unconjugated Hyperbilirubinemia[18]. It was observed by Maruo Y and Nishizawa K et al that the defects of UGT1A1 were an underlying cause of the prolonged unconjugated hyperbilirubinemia associated with breast milk. One or more components in the milk may trigger the jaundice in infants who have such mutations[19].

CONCLUSION

Although many maternal & fetal factors influence the serum bilirubin levels during neonatal period gender also shows its effect. In our study there was no significant difference in maternal age, gestational age, and birth weight, perinatal age between female and male infants. In accordance to other studies the total bilirubin levels were high both in female and male infants but the difference was statistically not significant. On the other hand the direct bilirubin levels in female infants were significantly high compared to male infants but less than 2mg/dl. In our study all the infants were exclusively breast fed. In conclusion, hyperbilirubinemia is common among the new born infants and is associated with breast feeding. In addition to other factors gender may also show the influence on bilirubin levels. Effect of Y chromosome, maternal hormones and gender difference in UDP-GT mRNA could be contributing factors for this.

ABBREVIATIONS

STB-serum total bilirubin, DB- direct bilirubin, UDP-GT- uridinediphosphate glucuronyltransferase

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