https://doi.org/10.5272/jimab.2022284.4660

Journal of IMAB
ISSN: 1312-773X
https://www.journal-imab-bg.org

Journal of IMAB - *Annual Proceeding (Scientific Papers).* 2022 Oct-Dec;28(4)

Original article

PRENATAL FACTORS FOR NEONATAL JAUNDICE

Tatiana D. Itova[1], Victoria A. Georgieva[2]
1) Department of Neonataoalgy, University Hospital Medica Ruse Ltd., Ruse, Bulgaria
2) Clinic of Neonatology, UMHATDr G. Stranski, Medical University, Pleven, Bulgaria.

SUMMARY:

Objective: To establish the role of prenatal factors for neonatal jaundice (NJ) in newborns (NB).

Material and methods: Retrospective study covering 566 mothers and their newborns, patients of University Hospital Medica Ruse, Bulgaria, from 01. 01. 2017 to 31. 10. 2020. The data were obtained from the documentation of the mother. Bilirubin (BR) levels were monitored by transcutaneous measurement with a KJ-8000 bilirubinometer .

Results: Significantly higher levels of BR are registered in NBs, whose mothers aged ≤20 years. History of NJ in siblings and hyperbilirubinemia in subsequent NB are moderately strongly correlated (p=0.025). First-born infants have significantly lower BR levels (p=0.037).

The BR levels of NBs whose mothers were at risk of premature birth were significantly higher. In infants of mothers with Preeclampsia, lower levels of BR are registered. We found a negative linear relationship between thyroid gland pathology and BR levels. We found a positive relationship between maternal urinary tract pathology and the manifestation of hyperbilirubinemia in NBs. A negative correlation was observed between maternal anemic conditions and NB hyperbilirubinemia. NBs of mothers with inflammatory diseases of the female reproductive system have significantly higher levels of BR.

Conclusion: Prenatal factors influencing NJ are maternal parity and age, as well as a history of jaundice in siblings. Inflammatory diseases of the reproductive system affect the degree of bilirubinemia, pathology of the urinary system increases its frequency. Well-controlled thyroid function and balanced iron supplementation in pregnant women help to better balance the metabolism of BR in full-term NBs. Preeclampsia diminishes the incidence of hyperbilirubinemia in full-term infants.

Keywords: newborn, neonatal jaundice, prenatal factors,

INTRODUCTION:

Neonatal jaundice (NJ) is a visual manifestation of yellow coloration of the skin, mucous membranes and sclera of the newborn (NB) due to increased levels of total bilirubin (BR) [1, 2]. Demographic, environmental and genetic factors have been identified as being at risk of developing severe neonatal hyperblirubinaemia (HB)[3]. Prenatal, intranatal, and postnatal effects may influence the evolution of NJ. Mother's knowledge, attitude, and behavior about the various aspects of NJ are significantly better in older than in younger women and significantly better with increasing birth rates, as well as in mothers with higher levels of education [4].

PURPOSE:

To establish the role of prenatal factors (sequence of pregnancy and childbirth, history of NJ in siblings and diseases during pregnancy) for the manifestation of NJ in NBs.

MATERIAL AND METHODS:

The study is retrospective, includes 566 mothers and their full-term infants who were patients of the Department of Obstetrics and Department of Neonatology of University Hospital Medica Ruse, Bulgaria, from January 2017 to October 2020. Data on the pathology of pregnancy were obtained from the documentation submitted in admission and medical history. Data on the manifestation of NJ are derived from the medical history of NBs. A transcutaneous measurement of total BR with a bilirubinometer KJ-8000 was performed as follows: from about 12th postnatal hour daily until discharge, on the 12-14th and 28th-30th postnatal day. Patient'spersonal data and test results were stored, processed, and presented in accordance with the Personal Data Protection Act.

The statistical processing was performed using the statistical processing program IBM SPSS Statistics version 23 and spreadsheet program, part of the MS Office package - Microsoft Excel version 2016. For the significance level, which rejects the null hypothesis, p≤0.05 was chosen.

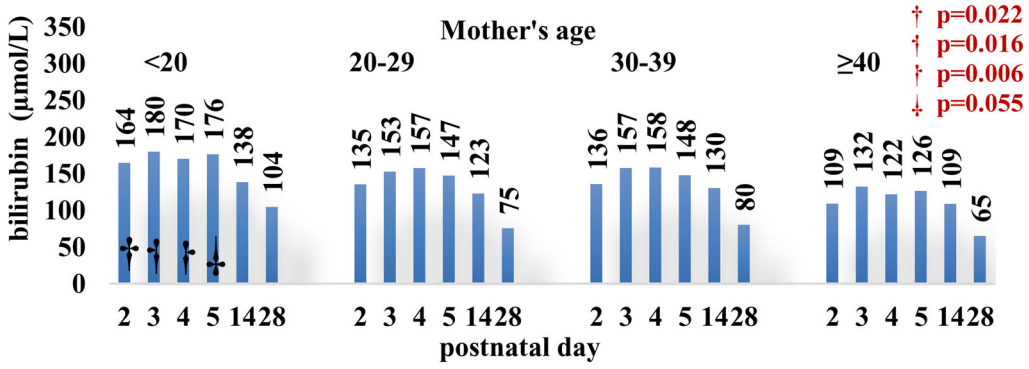
RESULTS:

The age distribution of mothers is shown in Table 1. Significantly higher levels of BR from the second to the fifth day (p=0.022, p=0.016, p=0.006, p=0.055) were registered in the group of mothers aged ≤20 years. We proved a statistically significant inverse weak linear relationship between the levels of BR on the second day in NBs and the age of the mother (r (362) = -0.112, p=0.033). No difference was found in the levels of BR in NBs when compared based on marital status, educational qualifications of the mother and place of residence. (Table 1, Fig. 1).

Table 1. Distribution of cases of NJ according to maternal factors (p≤0.05; r› - Spierman rank correlation coefficient, R² - coefficient of determination)

Index	*Groups(n)*		*NB with NJ(%)*	*p*	*r*	*R^2*
Age (in years) 28.8±5.1	*<20*	*13*	*41.3*	*2nd day 0.022*		*2.6%*
	20-29	*341*	*36.5*	*3th day 0.016*		*2.2%*
	30-39	*196*	*20.0*	*4th day 0.006*		*3.4%*
	≥40	*16*	*38.9*	*5th day 0.055*		*3.5%*
Marital status	*Married*	*332*	*41.0*	*NS*		
	Single	*230*	*36.1*			
	Another	*4*	*25.0*			
Education	*Primary*	*13*	*53.8*	*0.036*	*0.096*	
	Higher secondary	*356*	*34.8*			
	Tertiary	*197*	*45.2*			
Domicile	*District city*	*377*	*38.2*	*NS*		
	Town	*90*	*38.9*			
	Village	*99*	*41.4*			
Pregnancy (n)	*1*	*393*	*38.9*	*NS*		
	>1	*173*	*38.7*			
Birth (n)	*1*	*407*	*38.8*	*NS*		
	>1	*159*	*39.0*			
History of NJ in sibling	*Responded*	*146*				
	With NJ	*102*	*69.9*	*0.025*	*0.227*	

Fig. 1. Mean levels of total bilirubin values in newborns (μmol/L) according to the age of the mother by postnatal days



Multifactorial linear regression analysis of maternal demographics (age, place of residence, education, marital status) versus postnatal BR levels in their children showed a significant negative relationship between parturient age and BR of NB on the second day after birth (R^2, 1.3 CI, -1,660 ÷ -0.071, p=0.033). With regard to other demographic indicators, no significance was reported.

Confirmation of the presence of NJ in siblings gave 66.9% of multipara. Their newborns expressed higher levels of BR during the entire neonatal period (Tabl.1, Fig.2).

A moderately strong association was found between the history of NJ in siblings and the presence of HB in the next NB. Spearman rank correlation coefficient was calculated: (r›)-r› (98)=0.227, p=0.025. NB with previous siblings with NJ required phototherapy in 59.8% of cases, while those without such history – only in 29.5%.

Fig. 2. Mean level of total bilirubin values in newborns (μmol/L) according to a history of NJ in the previous sibling

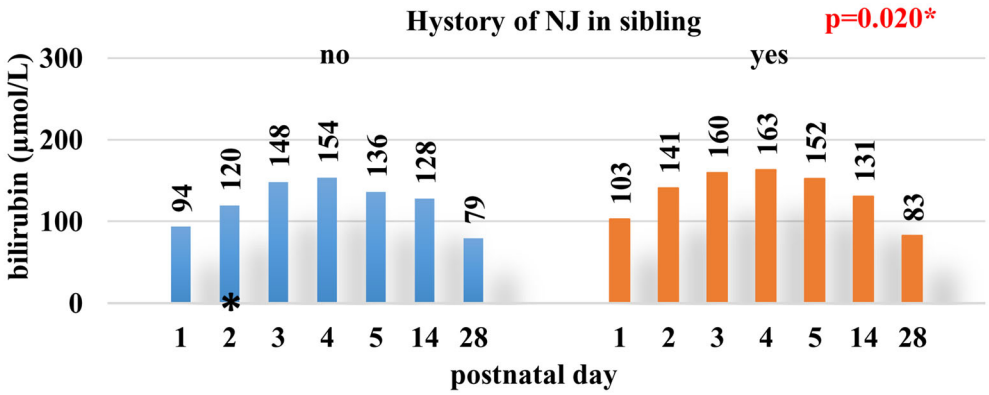


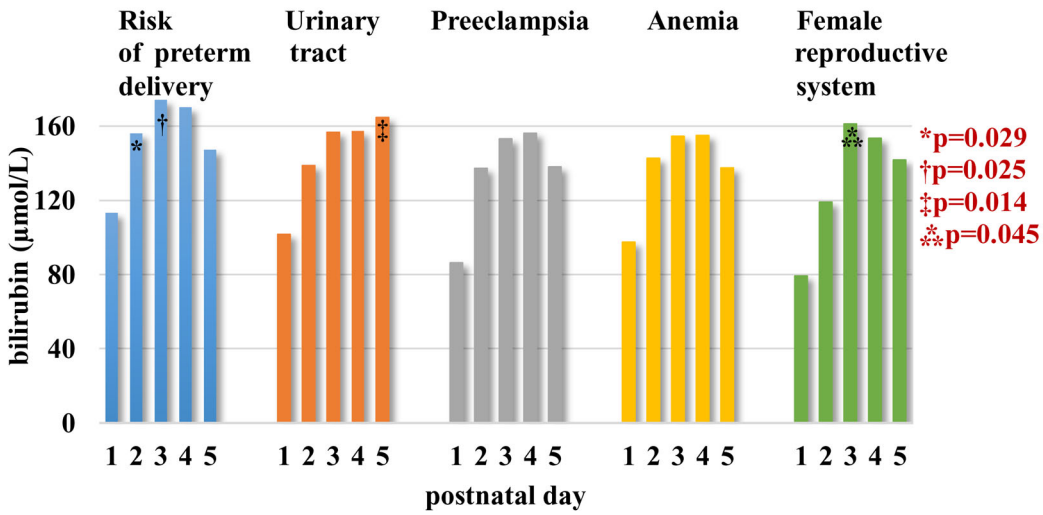
Table 2. Maternal diseases during pregnancy (*p≤0.05;R² - coefficient of determination)

Maternal diseases	*Number of mothers (% of all)*	*NB with HB in the relevant group (%)*	*p* (for BR level)*	*R²*
Risk of preterm delivery	***29 (5.1%)***	***34.6***	***2nd day 0.029** ***3th day 0.025***	***1.3%*** ***1.1%***
Thyroid gland	***41 (7.2%)***	***39.0***	***NS***	
Preeclampsia	***48 (8.5%)***	***33.3***	***NS***	
Anemia	***27 (4.8%)***	***37.0***	***NS***	
Female reproductive system	***17 (3.0%)***	***58.8***	***3th day 0.014****	***1.3%***
Urinary tract	***27 (4.8%)***	***48.1***	***5th day 0.014****	***1.3%***
All infections	***56 (9.9%)***	***48.2***	***NS***	
NB with HB from 1st to 14th days		***38.9%***		

71.9% of NBs were first born children. They had significantly lower BR levels on the fourth postnatal day (155.30±33.0 μmol/L) compared to those from second or consecutive births (163.7±30.9 μmol/L, p=0.037). Despite the established difference, the need for phototherapy in both groups was similar - 46.2% and 49.1%, respectively. Multifactorial linear regression analysis between BR levels in NBs and pregnancy sequence, birth sequence and history of HB showed significant values on the second (R^2, 8.90%; p=0.032) and fourth postnatal day (R^2, 8.2%; p=0.040).

Pathology of pregnancy with imminent premature birth in the last trimester, which required hospital treatment, was registered in 5.1% of mothers (Table 2). 34.6% of these mothers gave birth of children with HB. Mean BR values of these NB were significantly higher than in the other groups on the second (156.1±39.7 μmol/L) and third (174.2 ±47.6 μmol/L) postnatal day. The correlation between HB in NB and pathology with imminent premature birth is weakly positive (2nd day: r(360)=0.115, p=0.029; 3rd day: r(468)=0.103, p=0.025). (Table 2, Fig. 3)

Fig. 3. Mean level of total bilirubin values in newborns (μmol/L) according to maternal diseases during pregnancy.



Mothers who received therapy during pregnancy due to established hypertension or Preeclampsia consist 8.5% of the group. Their children have a lower incidence of HB (33.3%).

Pathology of the thyroid gland requiring thyroid hormone replacement therapy was found in 7.2% of the mothers. The incidence of HB in this group was 39%. We proved a statistically significant weak negative linear relationship between both indicators on the first day (r=-0.140, p=0.027).

2.8% of mothers suffered from urinary system pathology during pregnancy (hydronephrosis, calculosis, renal colic). HB was observed in 48.1% of their NBs. The correlation analysis showed a weak positive relationship between renal pathology during maternal pregnancy and the manifestation of HB in NB (r=0.116, p=0.014 on day 5).

Anemic conditions requiring treatment were found in 4.8% of the mothers, and 37% of their children suffered from HB. A weak negative correlation was observed between maternal anemic conditions during pregnancy and HB of NBs(r=-0.089, p=0.027 on day 3; r=-0.112, p=0.051 on day 5). No significant difference was found in mean bilirubin levels in newborns of anemic mothers(Fig.3), although they were lower compared to the other groups.

Inflammatory diseases of the female reproductive system, requiring systemic and local antimicrobial treatment, have been documented in 3% of cases. The NBs of these mothers had significantly higher BR levels on the third postnatal day (p=0.023). The performed correlation analysis showed a weak positive relationship (r=0.114, p=0.007 on the third day).

DISCUSSION:

The relationship between maternal age at birth and the occurrence of neonatal HB is insignificant, according to some studies [5]. Younger mothers, especially those under the age of 20, represent a higher risk of HB for their NB compared to the rest of the population [6]. Our study also demonstrated an inverse correlation between maternal age and BR levels in NBs.

According to our data, the mother's demographics (place of residence, marital status and education) are not related to the incidence of HB in their NBs. The organization of healthcare in Bulgaria assumes that births take place in hospitals, as the latter is available to all patients, and the newborns are monitored during the first three days in neonatology units.

There is a slight correlation between BR levels and maternal parity [5]. In our group of patients, the share of those born from the second or subsequent pregnancy is 1/3 of the total, and from the second or subsequent birth, slightly less than 1/3. We found significantly higher levels of total BR in children born from second or consecutive birth. However, the sequence of pregnancy did not correlate with bilirubin levels.

In NBs, whose larger siblings suffer from HB (BR>205 μmol/L), the risk of developing HB was 3.1 times higher. If the previous sibling expressed significant HB (BR >257 μmol/L), the risk in the next child increases to 12.5 times [7]. Najib K, et al. puts the history of severe HB in previous siblings in second place as a risk factor for the development of NJ [8]. A Danish study of a large number of births (19809) found a significant correlation between the incidence of NJ and peak levels of BR in siblings [9]. We found a moderate correlation with higher mean levels of BR and a higher proportion of phototherapy in NB whose older siblings had NJ.

Preeclampsia is not associated with neonatal HB [5]. In a study by Maisels M, et al. involving 2416 NB, no significant association of HB with Preeclampsia was observed [10]. Mosayebi Z, et al. assessed laboratory parameters in children born to mothers with Preeclampsia, only 39.2% reported the presence of HB [11]. In our study,the incidence of HB, requiring phototherapy, was lower in newborns born to mothers with Preeclampsia. Boskabadi H, et al., in several of the cited studies in their meta-analysis, reported that

hypertension and Preeclampsia during pregnancy often lead to NJ (4.7-19%) because high maternal blood pressure is an important factor for premature birth and premature babies are at high risk of developing jaundice due to hepatic immaturity and polyglobulia [12]. On the other hand, Preeclampsia stimulates the maturation of the fetal liver function. Therefore, full-term infants born to mothers with such pathology expressed lower levels of BR.

Uncontrolled maternal hyperthyroidism in the second half of pregnancy can lead to transient central hypothyroidism in NB [13]. Most, if not all, cases of transient congenital hypothyroidism are due to maternal autoimmune thyroid disease [13]. We did not find a difference in bilirubin levels in the NB of mothers treated for thyroid pathology; all mothers were in a euthyroid condition at birth. We registered a child with transient hypothyroidism who suffered from prolonged NJ. Íis mother had elevated antithyroglobulin antibodies.

Anemia in pregnant women is a high-risk factor for the pathological course of HB in NBs [14]. High doses of iron supplementation in pregnant women increase the incidence of physiological jaundice in NBs [15].Excess of iron influences hemoxygenase-1, which is responsible for converting heme to biliverdin. The latter, in turn, becomes BR and may increase the likelihood of NJ [16].

Delayed umbilical cord clamping is associated with increased iron transfer to the NB and also increased NJ frequency [17]. Children of anemic pregnant women in our group did not suffer more often from severe jaundice, which indicates adequate therapy. A weak negative correlation was observed between the presence of anemia in pregnant women and HB in the NB.

Manifestation of maternal infection during pregnancy is strongly associated with neonatal HB [5]. Premature rupture of the amniotic membranes is a significant factor in the manifestation of NJ [17,18], and 2.7% [13] of NJ cases are explained by it. Newborns whose mothers had an infection during pregnancy are more likely to suffer from NJ [19]. The incidence of NJ in such neonates is 3.45% [12] - 4% [20]. We reported a higher than average incidence of hyperbilirubinemia in children of mothers with inflammatory diseases of the female reproductive system (58.8% of NBs in this group), urinary system pathology (48.1% of NBs in this group) and infectious pathology (48.2% of all inflammatory diseases during pregnancy).

CONCLUSION:

According to our data, prenatal factors that may increase the incidence of NJ and BR levels in NB are parity, the history of jaundice in siblings, the younger age of the mother. Inflammatory diseases of the female reproductive system affect the severity of neonatal bilirubinemia, and pathology of the urinary system increases its frequency. Well-controlled thyroid function, as well as balanced iron supplementation of the pregnant woman, contribute to a better balance of neonatal BR metabolism. Preeclampsia and hypertension during pregnancy decrease the rate of HB in full-term infants.

REFERENCES:

1.Watchko JF. 84 - Neonatal Indirect Hyperbilirubinemia and Kernicterus. Part XV: Hematologic System and Disorders of Bilirubin Metabolism. In: Avery's diseases of the newborn. Editors Gleason CA,Juul SE. 10th ed. Elsevier. 2018, pp. 1198-1218.e5. [Crossref]

2. Keren R, Tremont K, Luan X, Cnaan A. Visual assessment of jaundice in term and late preterm infants. *Arch Dis Child Fetal Neonatal Ed.* 2009 Sep;94(5):F317-22. [PubMed]

3. Watchko JF. Identification of neonates at risk for hazardous hyperbilirubinemia: emerging clinical insights. *Pediatr Clin Nort Am*. 2009 Jun;56(3):671-87. [PubMed]

4. Al-Zamili AH, Saadoon ZA. Knowledge, Attitude and Practice of Mothers to Neonatal Jaundice. *Medico-Legal Update*. 2020 Jan-Mar; 20(1):1065-1070. [Internet]

5. Taneja S, Pande V, Kumar H, Agarkhedkar S. Correlation of various maternal factors with exaggerated hyperbilirubinemia of the newborn. *J Datta Meghe Inst Med Sci Univ*. 2017; 12(3):218-22. [Crossref]

6. Scrafford CG, Mullany LC, Katz J, Khatry SK, LeClerq SC, Darmstadt GL, et al. Incidence and risk factors for neonatal jaundice among newborns in Southern Nepal. *Trop Med Int Health*. 2013 Nov;18(11):1317-28. [PubMed]

7. Khoury MJ, Calle EE, Joesoef RM. Recurrence risk of neonatal hyperbilirubinemia in siblings. *Am J Dis Child.* 1988 Oct 1;142(10):1065-9. [PubMed]

8. Najib KS, Saki F, Hemmati F, Inaloo S. Incidence, risk factors and causes of severe neonatal hyperbilirubinemia in the South of iran (fars province*). Iranian Red Crescent Medical Journal*. 2013 Mar;15(3):260.

9. Nielsen HE, Haase P, Blaabjerg J, Stryhn H, Hilden J. Risk factors and sib correlation in physiological neonatal jaundice. *Acta Paediatrica Scand*. 1987 May;76(3):504-10. [PubMed]

10. Maisels MJ, Gifford K, Antle CE, Leib GR. Jaundice in the healthy newborn infant: A new approach to an old problem. *Pediatrics*. 1988 Apr; 81(4):505-11. [PubMed]

11. Mosayebi Z, Nariman S, Hosseini L, Movahedian AH. Evaluation Of laboratory disorders in admitted neonates in NICU who were born to preeclamptic mothers. *J Comprehensive Pediatrics*. 2013 Nov 1;4(4): 194-9. [Crossref]

12. Boskabadi H, Rakhshanizadeh F, Moradi A, Zakerihamidi M. Risk factors and causes of neonatal hyperbilirubinemia: a systematic review study. *J Pediatr Rev*. 2020 Oct 1;8(4): 211-22. [Crossref]

13. Lee YS, Loke KY, Ng SC, Joseph R. Maternal thyrotoxicosis causing central hypothyroidism in infants. *J Paediatr Child Health.* 2002 Apr;38(2):206-8. [PubMed]

14.Komovzova AA, Kovaleva YuA. [Anemia of pregnancy as a risk factor for the development of severe

course of neonatal jaundice.] Collection of theses of the All-Russian scientific-practical conference with international parts. St. Petersburg State Paediatric Medical University. 2019. [in Russian].

15. Moghimi MA, Malekzadeh J, Moghimi M. An assessment of the relationship between maternal iron supplementation and hyperbilirubinemia in neonates: a nested case-control study. *Int J Adv Bio Technol Res*. 2017 Jan 1;8(4):1573-78.

16. Maines MD, editor. Current protocols in toxicology. John Wiley. 2020.

17. Mesiæ I, Milas V, Meðimurec M, Rimar Z. Unconjugated Pathological Jaundice in Newborns. *Coll Antropol*. 2014;38(1):173-178. [Internet]

18. McDonald SJ, Middleton P, Dowswell T, Morris PS. Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes. *Cochrane Database Syst Rev*. 2013 Jul 11;2013(7):CD004074. [PubMed]

19. Garosi E, Mohammadi F, Ranjkesh F. The relationship between neonatal jaundice and maternal and neonatal factors. *Iranian Journal of Neonatology*. 2016 Mar;7(1, S1):37-40. [Crossref]

20. Korejo HB, Bhurgri GR, Bhand S, Qureshi MA, Dahri GM, Chohan RK. Risk factors for kernicterus in neonatal jaundice. *Gomal Journal of Medical Sciences*. 2010; 8(1):12-5.

Please cite this article as: Itova TD, Georgieva VA. Prenatal factors for neonatal jaundice. *J of IMAB*. 2022 Oct-Dec;28(4):4660-4665. DOI: https://doi.org/10.5272/jimab.2022284.4660

Received: 28/02/2022; Published online: 07/11/2022

Address for correspondence:
Tatyana Itova
University Hospital Medica Ruse, Ruse,
35, Riga Str., Ruse, Bulgaria.
E-mail: taniaitova@abv.bg