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Jaundice in full-term newborns – frequency, etiology, prophylaxis, follow-up

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The dissertation work consists of 176 pages, 2 annexes and is illustrated with 46 figures and 26 tables. The bibliographic list includes 306 literary sources, of which 14 in Cyrillic and 292 in Latin.

The dissertation paper was discussed and proposed for protection by the Extended Department Council of the Department of Pediatric Diseases at the Medical University, Pleven on July 14, 2023 and directed for protection before a Scientific Jury.

The materials related to the protection are available at the Scientific Department of the Medical University – Pleven.

Thanks to my scientific advisor Assoc. Prof. Dr. Victoria Atanasova, MD, PhD for her unreserved and continuous support, for her guidance and inspiration, for her patience and humanity.

CONTENT:

ABBREVIATIONS USED:

Abbreviation	***Full name***
PN	birth by normal mechanism
SC	birth by operating mechanism
BR	bilirubin
URT	upper respiratory tract
FRS	female reproductive system
UTI	urinary tract infection
NJ	neonatal jaundice
NB	newborn
OBE	acute bilirubin encephalopathy
TBR	total bilirubin
PaNJ	pathological neonatal jaundice
PB	probiotic
PrNJ	prolonged neonatal jaundice
SF	standard formula
PhNJ	physiological neonatal jaundice
PhT	phototherapy
HB	hyperbilirubinemia
HDN	hemolytic disease of the newborn

I. INTRODUCTION

Neonatal jaundice is a common condition in the first days of life and usually manifests as a visible yellow tinge of skin and mucous membranes. It is usually benign during the neonatal period. In some newborns, unconjugated bilirubin can reach dangerous levels and cause acute bilirubin encephalopathy and permanent neurological damage when the condition is not recognized and treated in time.

In practice, the recognition of hyperbilirubinemia is based on visual inspection of the skin, followed if necessary by the quantification of total serum bilirubin and its fractions. Assessing the risk factors that can affect the severity of hyperbilirubinemia is an important point to build a behavior strategy. For our country there are no studies on the assessment of risk factors in the newborn and the mother for the manifestation of neonatal jaundice. In practice, the recommendations of the American Academy of Pediatrics are most often used due to the lack of such made for Bulgaria.

The meturing of transcutaneous bilirubin is not commonly used in outpatient practice in our country, although this is the most painless and accessible way to measure it. For the Bulgarian newborn population, there are no studies on the evolution of bilirubinemia, and there is no nomogram for bilirubin changes during the neonatal period to be used in everyday practice. The use of nomograms made for children born in other countries and at other latitudes and growing conditions is not sustainable, as there are regional and racial differences in the dynamics of bilirubinemia in newborns.

Most of the studies on which the conclusions are based on are about the incidence and type of neonatal jaundice are on its more severe forms, requiring additional hospitalization and treatment. Therefore, these studies do not give a full scope to the problem of neonatal jaundice and a real assessment of its incidence and prevalence. More methodical and systematic analyses of the jaundice in newborns are needed to assess the need for treatment.

Today, the methods of therapy of neonatal jaundice are unified. For the past 60 years, modern phototherapy lamps have been developed and this is the gold standard for its treatment at the moment, although the surgical methods have not lost their relevance. After the introduction of intensive phototherapy in Bulgaria in the late 90‘s, the frequency of exchange blood transfusions was reduced and complications of severe hyperbilirubinemia on the one hand, and surgical intervention on the other, were prevented accordingly.

However, there are fewer observations and scientific reports in the prevention of neonatal jaundice. Today, the results of research on the application of probiotics in many different directions to improve human health are published. Whether prophylaxis with

probiotics could prevent the development of severe hyperbilirubinemia – there is still no answer to this question.

Prolonged neonatal jaundice is always an occasion for additional research and consultations. It is the most common reason for outpatient examinations in newborns. What is the frequency and etiology of this type of jaundice for our population there is no literature data.

The stated prerequisites determined the choice of the topic of the present dissertation work.

II. GOAL AND OBJECTIVES

Objective: To study in term newborns the frequency, etiology and dynamics of NL due to indirect hyperbilirubinemia, to evaluate the effect of prophylactic administration of probiotic strains on its evolution and to follow the influence of NL on neuropsychological development up to 6- monthly age.

Tasks:

Task 1. To establish the frequency and etiological structure of Pathological neonatal jaundice and prolonged neonatal jaundice in full-term newborns.

Task 2. To study the influence of certain demographic and perinatal factors on the manifestation of Pathological Neonatal Jaundice and Prolonged Neonatal Jaundice in full-term newborns.

Task 3. To monitor the dynamics of total bilirubin in full-term newborns until reference limits are reached in order to develop a nomogram..

Task 4. To study the effect of prophylactic application probiotics for the prevention of neonatal jaundice.

Task 5.To monitor the neuropsychiatric development, weight curve and hemoglobin levels of newborns with prolonged neonatal jaundice until the age of six months.

III. MATERIAL AND METHODS

Material

1. Location of the study

This study was conducted from January 2017 to November 2020 in the Department of Neonatology at the University Hospital "Medica Ruse" Ltd.

2. Financing of the study

The present study has no special funding.

3. Ethical aspects of the study

The model of the study has received approval from the Ethics Committee at Medical University-Pleven and the University Hospital "Medica Ruse" Ltd. Patients' personal data and test results were stored, processed and presented in accordance with the Personal Data Protection Act.

4. Study design

The study is ambitious (two years retro- and two years prospective) and controlled. The survey was conducted from January 2017 to November 2020 in the Department of Neonatology at the University Hospital "Medica Ruse" Ltd. Full-term NB survivors of the neonatal period are covered.

Included are full-term newborns who meet the International Classification of Diseases and Related Health Problems 10th revision – born at the gestation term from 37 full weeks to less than 42 full weeks (259 to 293 days).

Initially, 919 NB were covered, of which 65 were weighing less than 2500 grams and/or under the age of 37 weeks. The patient selection process is reflected in Fig. 1.1. Table 1.1 presents the criteria for inclusion of patients. A total of 288 NB were dropped out of the observation, of which 2 children were excited during the late neonatal period, 2 children were in need of urgent surgical intervention, one with chromosomal aberration and 283 NB with an incomplete amount of information. The remaining 566 NB are included in the current study.

Methods

1. Documentary methods

The data of the patients (anamnestic, clinical, laboratory, anthropometric) are entered in a specially designed unified patient card No1 and No2 (Appendix No1 and Appendix No2) which contain information about:

- ✓ newborn: sex, gestational age, season of birth, birth weight, blood group;
- ✓ mother: age, place of residence, education, marital status, blood type, history of life and pregnancy;
- ✓ birth: mechanism, indications of operative birth, assessment by Apgar;
- ✓ diagram for bilirubin levels;
- ✓ additional laboratory tests conducted on NB;
- ✓ clinical observations and conducted therapy of NB;
- ✓ diet;
- ✓ follow-up of NB after discharge;
- ✓ duration of observation;
- ✓ outcome and final diagnosis;
- ✓ assessment of neuro-mental development up to 6 months of age;
- ✓ anthropometric data up to 6 months of age.

2. Diagnostic methods

2.1. Clinical methods

History of pregnancy and childbirth – the data are derived from the anamnesis taken from the mother upon admission for childbirth, as well as the accompanying documentation: medical history and outpatient lists, laboratory and imaging tests to support a history of pregnancy. Included indicators are: sequence of pregnancy and childbirth, neonatal jaundice in older siblings of the newborn, profession, place of residence, marital status of the mother, concomitant diseases before and during pregnancy, mechanism of current birth, season of birth.

Physical status of the newborn – height and birth weight and tracking of weight up to 6 months of age; visual assessment of neonatal jaundice according to Kramer's scheme, assessment of neuro-mental development with developmental coefficient (CoD) according to "Methodology for the study of intellectual development from birth to 3 years of age" by Manova-Tomova and BIND-M (Modified bilirubin induced neurologic dysfunction score).

Kramer's scheme for visual assessment of jaundice is a tentative method for assessing the degree of manifestation of NJ. In the event of icterus on the face, the BR is about 100 μmol

/L – this is zone 1. For each subsequent zone at cephalocaudal spread, add 50 μmol/L. The distinct zones are: Zone 2 – chest (100 μmol/L), Zone 3 – abdomen (150 μmol/L), Zone 4 – upper and lower extremities (200 μmol/L), Zone 5 – palms and feet (250 μmol/L). In the case of icterus spread in zone 3 and below, it was conducted and transcutaneous measurement of BR and when found to be overvalue, serum levels of BR with fractions are tested.

The coefficient of development includes the indicators of motor skills, sensory activity, emotional-social development and speech development. A table from Appendix 2 was used for the assessment. Data were taken from parents during ambulatory follow-up monthly from 1st to 6th month. The performance of one indicator has a value of one. CoR is calculated according to the following formula: **CoD = MA/CA*100**, where MA is established mental age, CA is calendar age. The values of CoD are interpreted as follows: over 120 – very preemptive mental development, 110-119 – pre-emptive; 90-109 – normal; 80-89 — lagged; 70-79 — borderline.

Coefficient BIND-M assesses the impact of bilirubinemia on the neurological status of the newborn. In his calculation are included the parameters: mental state, muscle tone, crying and change in gaze. BIND-M was calculated at a prophylactic examination at postnatal day 14 or at current status on the day of rehospitalisation if treatment for PrNJ was required. Each indicator receives a score of 0 to 3 points, which are summed up. The interpretation of the results is as follows: 1-4 – mild acute bilirubin encephalopathy, 5-6 – moderate, ≥7 – severe and very severe.

Gestational age was determined by maternal amenorrhea and morphological criteria – New Ballard Score.

New Ballard Score is a method for determining gestational age by physical and neurological criteria. Neuromuscular criteria include: posture, square window, reverse flexion of the hand, kneel angle, scarf symptom, heel to ear symptom. The physical criteria that enter into the evaluation are: skin transparency, lanugo spread, plantar surface striation, mammal development, ear cartilage and ocular fissures, genital development. Each of the above criteria is rated from 0 to 5. The results obtained are added together. They are then compared with the nomogram compiled by D-r Jeanne L Ballard for calculation of gestational age.

Apgar assessment – a method for assessing the state of NB after childbirth, which includes 5 indicators – muscle tone, heart rate, reactivity, skin color, breathing. Each of them is evaluated from 0 to 2 points, then the points are added together. The data is reported at the first and fifth minutes of birth. According to the ICD – the 10th revision of the first minute score 7-

10 indicates normal adaptation, 4-6 responds to moderate asphyxia, and 3 or less – severe asphyxia.

2.2. Laboratory methods

All tests of hemo- and urine parameters have been carried out in the Clinical Laboratory at the University Hospital "Medica Ruse" Ltd. – complete blood count (CBC) total and direct bilirubin, liver enzymes (ASAT, ALAT) serum iron, urine analysis by automatic analyzers as follows:

- Blood count – Hematologic Analyzer BC-5800, Mindray, China;
- Blood glucose – Glucose analyzer BIOSEN C line, EKF Diagnostic, England;
- Total bilirubin, Direct bilirubin, Serum iron – Centrifuge MPW-223, Germany and Automatic Biochemistry Analyzer BA 400, BioSystems, Spain;
- Urine analysis – Urine analyzer DURU H 500 Cr

The reference values of the monitored chemo- and urine performance of the laboratory are reflected in Table. 1.

1.3. Instrumental methods

- Transcutaneous bilirubinometry – BR was measured in μmol/L on the forehead of NB by transcutaneous bilirubinometry with bilirubinometer KJ-8000. The first measurement is about 12 hours after birth, then daily is carried out until leaving the neonatal dapartment, then between the 12th and 14th day and the 28th and 30th day. If tanscutaneous BR levels were found above the reference values for the respective day, these were confirmed by examination of serum BR levels with fractions. When the NJ was prolonged was continued with the follow-up until physiological values of BR were reached. The bilirubin meter is placed on the forehead of NB, avoiding areas of bruising or congenital skin changes. Three measurements were made and the average was recorded. Before each new measurement, the apparatus was calibrated. If NB was on phototherapy, bilirubinometry was performed about 12 hours after the end of the procedure, also on the forehead. To assess the need for therapy in established NB we used a nomogram for the treatment of hyperbilirubinemia by phototherapy of the American Academy of Pediatrics, as there is no accepted one for Bulgaria. An upper limit value for transcutaneous BR is marked above 171 μmol/L (10 mg/dL) on day 14 and 85.5 μmol/L (≥5 mg/dL) after day 28 of birth.

Table. 1. Reference values of the monitored parameters for Clinical Laboratory at the University Hospital "Medica Ruse" Ltd.

	Indicator	***Reference values***	***Measuring units***
1	Blood count (for a newborn): Leukocytes (WBC) Erythrocytes (RBC) Hemoglobin (HGB) Hematocrit (HCT) Platelets (PLT) PKK (for 6 months of age): Leukocytes (WBC) Erythrocytes (RBC) Hemoglobin (HGB) Hematocrit (HCT) Platelets (PLT)	 9.0-34.0 4.5-7.0 140-250 0.45-0.65 140-440 4.5-13.5 3.8-5.3 110-150 0.33-0.41 140-440	 10^9/L 10^12/L g/L l/1 10^9/L 10^9/L 10^12/L g/L l/l 10^9/L
2	Bilirubin: Total bilirubin Direct bilirubin	 1st day – up to 80 2nd day – up to 130 3rd day – up to 165 4th day – up to 200 5-8th day – up to 200 9-10th day – up to 165 28th day – up to 80 Newborns 0-7.6 28th day 0.1-3.4	 µmol/L
3	Serum iron	9-28	µmol/L
4	Urinalysis - test strip Specific weight pH Egg white Glucose Bilirubin Urobilinogen Ketotella Blood Sediment from urine	 1.010-1.030 5-7 Negative Negative Negative Unmagnified Negative Negative Up to 5 WBC and 5 RBC/field	

To verify transcutaneous bilirubinometry, we compared serum levels of total BR and transcutaneous levels of measured BR in a total of 262 samples, of which 176 were taken before or without phototherapy and 86 taken after 12 hours after phototherapy. The degree of

correlation between serum and transcutaneous levels of total BR was significative, the Pearson correlation coefficient from day 1 to day 4 before phototherapy being 0.435, 0.954, 0.859 and 0.790, respectively, and after PhT from day 2 to day 5 was 0.787, 0.832, 0.702 and 0.820 respectively (*Table. 2).*

- Anthropometry – measuring height and weight. A Seca 207 growth meter and an electronic scale Seca 384 were used.

- Ultrasound examination – ultrasound examination of abdominal organs was carried out with the Chsison Q9 apparatus.

Table. 2. Comparing serum and transcutaneous levels of total bilirubin before and after PhT (μmol/L)

	Day	***Trial***	***Count***	***Bilirubin (μmol/L)***	***Pearson Correlation***	***P***
Before PhT	**1**	with*	84	115.1±23.7	0.435	<0.001
		Tc*	84	118.7±22.5		
	2	with	48	157.1±37.0	0.954	<0.001
		Tc	48	163.3±40.8		
	3	with	34	177.9±27.4	0.859	<0.001
		Tc	34	180.0±25.5		
	4	with	8	201.8±21.4	0.790	0.020
		Tc	8	189.0±23.3		
		Total	**176**			
After PhT	**2**	with	18	167.7±20.9	0.787	<0.001
		Tc	18	164.8±25.2		
	3	with	29	189.8±40.7	0.832	<0.001
		Tc	29	196.8±34.3		
	4	with	27	191.9±33.8	0.702	<0.001
		Tc	27	181.3±19.9		
	5	with	12	192.2±30.9	0.820	0.001
		Tc	12	179.3±23.9		
		Total	**86**			
Total samples			**262**			
**c – serum level of total bilirubin;* tc – transcutaneous level of total bilirubin*						

2. Prophylactic methods

- Application of probiotics

In order to prevent NJ to feeding with a standard formula for newborns, we added a probiotic. Firstintake of PB is administered up to 12 hours after birth with established enteral nutrition and spontaneous defecation of NB. The application and dosage of the preparation is according to the manufacturer's instruction. It is continued afterwards with a daily single dose.

Our choice of PB is based on several requirements:

- ✓ To be easy, the amount of dose and the method of application to be suitable for newborns. That is why we chose the drop form, as the volume is small and easily applicable. The other method of intake, which is easy and suitable, is a factory-added probiotic strain to the formula for feeding newborns.
- ✓ To contain a single probiotic strain of bacteria to objectively compare the effect. Not to contain other additives (prebiotics, postbiotics, vitamin D).
- ✓ Probiotic strain should be recommended by the manufacturer as suitable for newborns and therefore have a dose for newborns.
- ✓ The type of bacteria that is taken should be consistent with the normal settlement of the gastrointestinal tract of the newborn with bacterial flora.
- ✓ The preparation containing PB should be available in Bulgaria.

The patients to whom we administered PB were divided according to the diet and the type of probiotic strain taken into the following groups:

Group A – 24 NB fed standard formula (SF) for NB and intake of Lactobacillus rhamnosus for the first 5 days at a dose of 6 drops orally, containing 6 x 10*9 GFU;

Group B – 16 NB fed SF and Lactobacillus reuteri intake during the first 5 postnatal days at a dose of 5 drops orally containing 100 x 10*6 CFU;

Group C – 18 NB fed SF and intake of Bifidobacterium animalis during the first 5 days at a dose of 6 drops orally containing 1 x 10*9 CFU;

Group D – 16 NB fed SF and added intake of Lactobacillus rhamnosus during the first 30 days at a dose of 6 drops orally containing 6 x 10*9 GFU;

Group E – 31 NB fed NB formula factory enriched with Lactobacillus reuteri during the first 30 days, containing about 115 x 10*6 CFU / 100 mL;

Group F – 17 NB fed SF and added intake of Bifidobacterium animalis during the first 30 days at a dose of 6 drops of orally containing 1 x 10*9 CFU;

Group G – 193 NB who took SF for food without added PB for the first 30 days.

A standard formula is a breast milk substitute specially produced to satisfy in itself the nutritional needs of infants during the first months of life until the introduction of appropriate supplementation feeding.

2. Therapeutic methods

- Phototherapy – performed with an intensive care lamp with blue LED light BC 250,000 with the possibility of 360-degree irradiation and uniform distribution of light throughout the body of NB. The child is placed undressed on the mattress of the lamp, with the genitals covered with a diaper and the eyes with a protective mask. Every three hours, NB is fed/breastfed and the covering blindfold is displaced.

3. Statistical methods

The data were entered and processed with SPSS 23.0 statistical package and Excel for Windows. For a significance level at which the null hypothesis is rejected, $p < 0.05$ was chosen. The following methods were applied:

- Descriptive analysis of quantitative and qualitative data – usedto classify the data and to obtain their summarized characteristics; calculation of frequency, arithmetic mean, standard deviation, minimum and maximum value, percentiles;
- Statistical tests to establish statistically significant difference – t-test, t-test for independent samples;
- Variance analysis – one-factor variance analysis ANOVA; one-factorisn variance analysis ANOVA with post hoc analysis;
- Correlation analysis to determine the strength of the relationship between two variables – Pearson's correlation coefficient; Spearman's correlation coecient, analysis of interval and nominal variable with eta (η) coecient, analysis of nominal variables with χ^2- test;
- Linear regression analysis to measure the degree of linear relationship between two or more variables;
- Graphical analysis – tables and figures were produced for visualization of the results obtained.

IV. RESULTS

<u>Task 1.</u> To establish the frequency and etiological structure of PaNJ and PrNJ in full-term newborns

Initially, 919 NB were covered, of which weighing less than 2500 grams and/or under 37 weeks of age were 65 NB. Tthe process of selection of patients is shown in Fig. 1.1. In Table 1.1. the criteria for patient inclusion are presented. A total of 288 NB were dropped from the observation, of which 2 children were excited during the late neonatal period, 2 were in need of urgent surgical intervention, one with chromosomal aberration and 283 NB with an incomplete amount of information. The remaining 566 NB are included in the present study.

Randomized in the current study were 566 newborn children, of which 274 were girls and 292 were boys. From 1 to 14 days in 146 NB (25.8%) of the observed did not manifest NJ, and in 200 (35.3%) manifested one with a physiological (PhNJ) characteristic. Pathological NJ (PaNJ) during the first two weeks was recorded in 220 (38.9%) of newborns. Prolonged (PrNJ) after day 14 postpartum was present in 82 (14.5%) of children. (*Fig. 1.2.*).

Table. 1.1. Criteria for the selection of participants in the study

Inclusion criteria :
• Gestational age at birth ≥37weeks. and birth weight ≥2500 g • Follow-up of NB to the 30th postnatal day or to involution of neonatal icterus
Exclusion criteria :
• Need for surgical treatment during the follow-up period • Exitus lethalis during the neonatal period • Congenital chromosomal diseases and inborn errors of metabolism • Gestational age at birth <37 weeks and/or birth weight <2500 g • Mixed feeding of the newborn • Incomplete patient follow-up period data

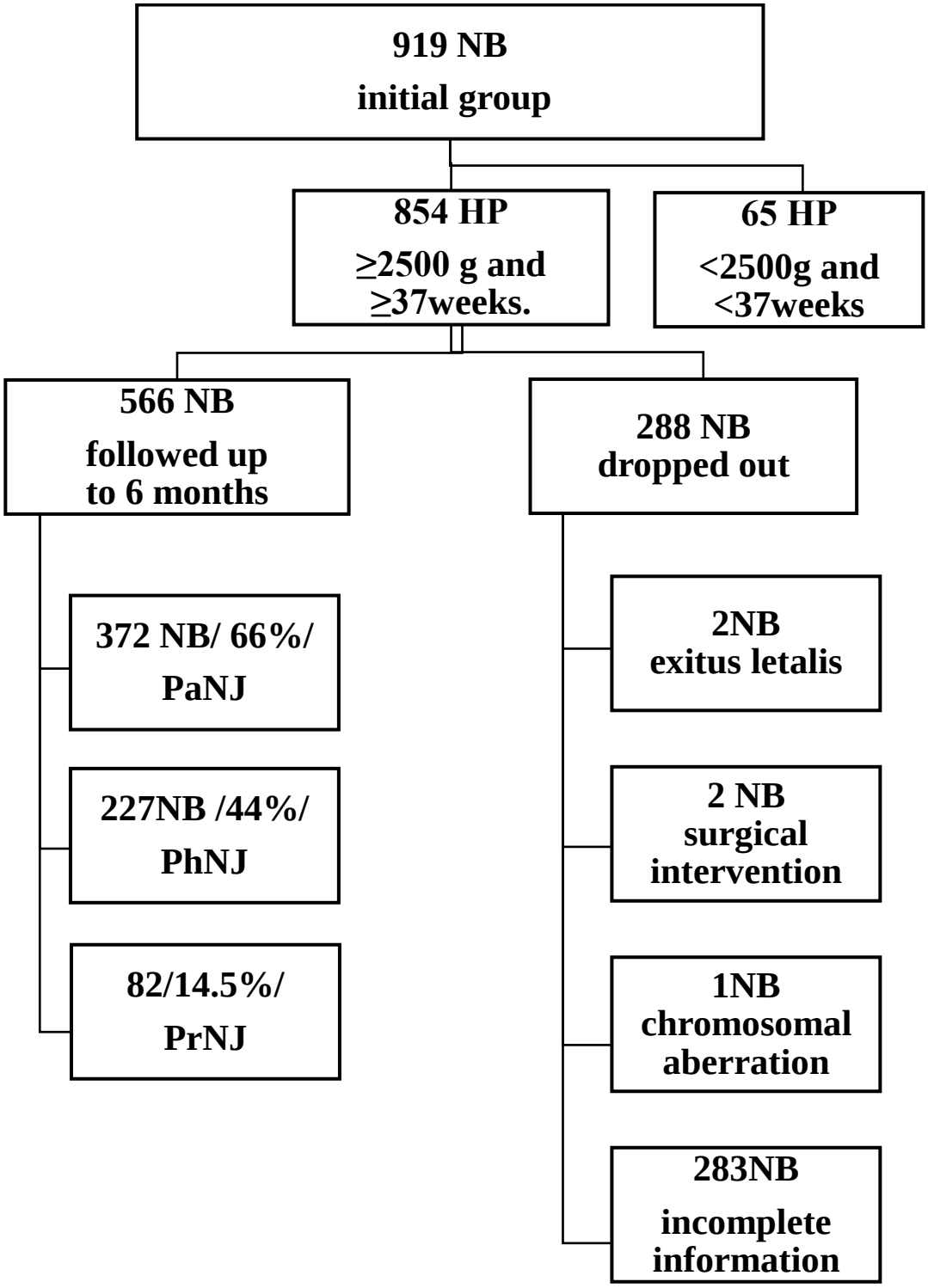

Fig. 1.1. Presentation of the process of selection of patients

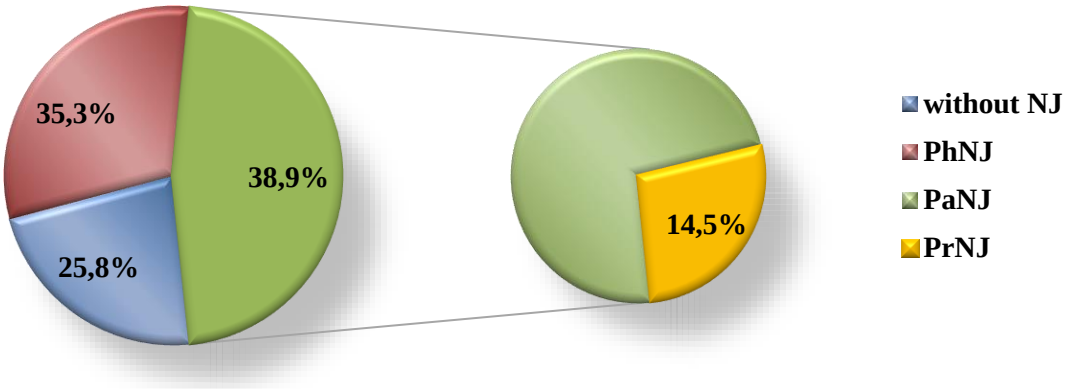

Fig. 1.2. Total distribution of types of NJ in % (NJ – neonatal jaundice; PhNJ – physiological neonatal jaundice; PaNJ – pathological neonatal jaundice; PrNJ – prolonged neonatal jaundice)

PaNJ occurs on the first postnatal day in 112(19.8%) of children and its share marks a decreasing trend in the following days (from 88/15.5% on the second day to 13/2.3% on the fifth day). PhNJ on the second day is registered at 216(38.2%) of NB, on the third day its share almost doubles, and on the 4th and 5th day slightly more than half of the NB have such a form of NJ. Without expression of NJ on the 1st postnatal day are 454(80.2%) of NB, after which their share decreases almost double on the second and third day (*Fig. 1.3.*).

Without clinical manifestation of NJ on the 14th postnatal day are 313(55.3%) of the observed children, in 185(32.7%) there are still PhNJ and 68(12.0%) have PaNJ. At the end of the neonatal period, 82(14.5%) of patients in the observed cohort had PrNJ. This percentage marks a decreasing trend (from 7.5% on the 45th day to 1.2% on the 75th day), and by the 90th postnatal day no more icterus is registered in the children in the NB group covered (Fig. 1.3.).

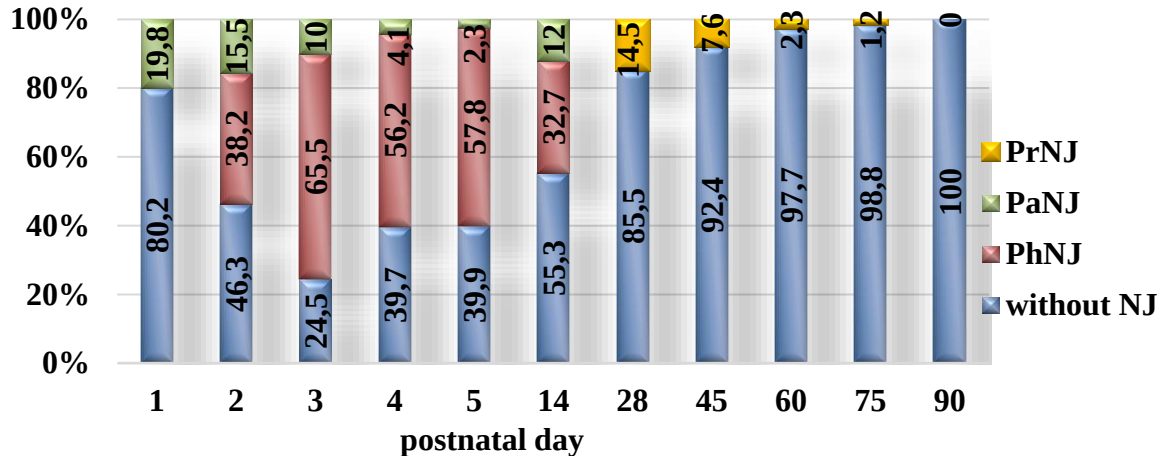

Fig. 1.3. Distribution of forms of NJ for the observation period (in %).

On table 1.2. is presented the etiological structure of PaNJ for the early neonatal period. The largest share is occupied by NJ from hemolysis due to blood-group incompatibility (ABO and Rh) – 79 NB (35.9%, of which 25.5% have ABO- and 10.4% have Rh incompatibility) and NJ in the course of intraamniotic infection – 51 NB (23.2%), 28 NB (12.7%) etiology was not established. In two cases, a combination of three etiological factors (intraamniotic infection, birth trauma with bruising and acidosis) was observed, and in 34 cases – a combination of two etiological factors. Most often it is a hemolytic form of NJ by ABO-/Rh-isoimmunization in combination with intraamniotic infection, polycythemia or hypoglycaemia. Other forms include respiratory distress syndrome (two children), diabetic fetopathy (two NB), transient hypothyroidism (1 NB) and giant hemangioma (1 NB).

Table. 1.2. Etiological structure of NJ in 220 newborns with PaNJ

№	***Diagnosis***	***n (%)****
1	**ABO-, Rh-isoimmunization**	**79 (35.9%)**
2	**Intraamniotic infection**	**51 (23.2%)**
3	**Polycythemia / Intrauterine hypotrophy**	**23 (10.5%)**
4	**Hypoglycemia / Dehydration**	**17 (7.7%)**
5	**Asphyxia / Acidosis**	**12 (5.5%)**
6	**Bruising / Cephalhematoma**	**11 (5.0%)**
7	**Other forms of hemolysis**	**7 (3.2%)**
8	**Meconium delayed evacuation**	**6 (2.7%)**
9	**Other****	**6 (2.7%)**
10	**Roving**	**28 (12.7%)**

** Some newborns have more than one cause of PaNJ;*

***Others: Respiratory distress syndrome, Giant hemangioma, Transient hypothyroidism, Diabetic fetopopathy*

In addition to blood-group isoimmunization, other hemolytic causes of PaNJ were recorded in another 41 NB (37.2%), their distribution is: Polycythemia / Intrauterine hypotrophy – 23 NB (10.5%), birth trauma with bruising / cephalhematoma – 11 NB (5.0%), and other forms of hemolysis – 7 NB (3.2%). In total, all hemolytic forms account for 73.1% of PaNJ.

PaNJ as a consequence of Hypoglycemia / Dehydration is registered in 17 NB (7.7%), Asphyxia / Acidosis – in 12 NB (5.5%), Delayed evacuation of meconium – in 6 NB (2.7%) .

In 82(14.5%) children of the observed cohort, the NJ was protracted and we established criteria for PrNJ. The analysis of the etiological structure of PrNJ at day 28 (*Fig. 1.4.*) showed that the largest proportion occupied by jaundice in exclusively breastfed babies who had digestive problems – 57% (12% had overweight gain; 21% had frequent vomiting or a clinic of gastroesophageal reflux; 13% had unsatisfactory weight gain for the first month; and 11% had irregular defecation or had obstipation). Hemolytic type PrNJ occurs in 19% of cases (9% – blood-group incompatibility; 8% – resorption of soft tissue hematomas from birth traumatism, 2% – polycythemia).

Other forms of PrNJ (4%) include one child with giant hemangioma, one with transient hypothyroidism, one with diabetic fetopathy and one with congenital cardiac malformalion (hemodynamically significant interventricular defect).

In 11 children (12% of the monitored population) with PrNJ, abdominal ultrasound examination showed a congenital anomaly of the collector part of the excretory system without proven underlying urinary tract infection during the neonatal period, as well as another cause of NJ.

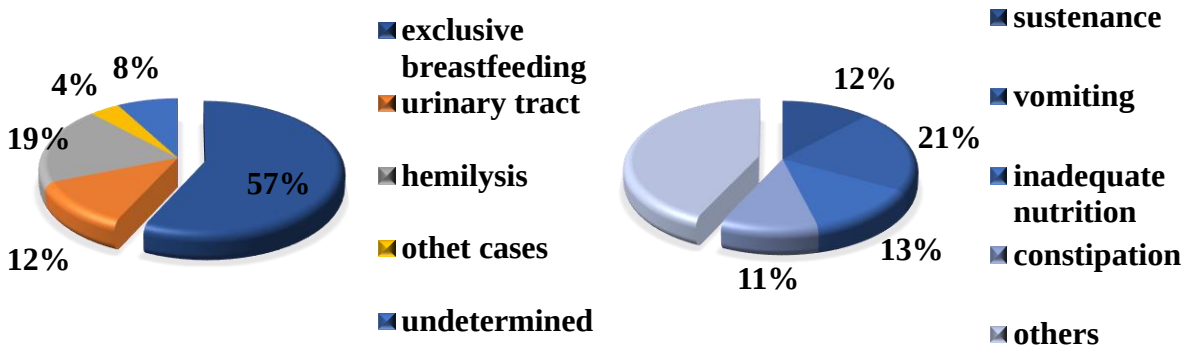

Fig. 1.4. Etiological structure of PrNJ (in %) at day 28 in the PrNJ group

Ultrasound examination of children with PrNJ at the age of 28 days and at 6 months was performed and screening for an underlying infection of the urinary system was performed. In 11 children (12% of the group) an abnormal structure in the urinary system was proven – from unilateral or bilateral mild pyelektasia to hydronephrosis I-II degree and dilation of ureter (3 children have I-II degree hydronephrosis) without detecting an underlying infection of the urinary system during the neonatal period. In only one child with unilateral hydronephrosis I-II degree at 6 months of age, a progression of the congenital abnormality was recorded and an underlying uroinfection was detected. In 8% of cases with PrNJ, the cause was

not established. Three children, from the group with hemolytic type PrNJ, at one year of age, were diagnosed with thalassemia minor.

Conclusion

According to our data, a leading cause of PaNJ in the early neonatal period is hemolysis due to ABO blood-group incompatibility. The largest share in the structure of PrNJ are exclusively breastfed NB with digestive problems. Despite the established abnormalities in the structure of the excretory system in NB with PrNJ, we did not find an accompanying urinary tract infections as a reason for prolongation of NJ.

<u>Task 2.</u> To study the influence of certain demographic and perinatal factors on the manifestation of Pathological neonatal jaundice and Prolongated neonatal jaundice in full-term newborns

2.1. Maternal factors:

2.1.1. Maternal demographic factors:

2.1.1.1. Maternal age:

In our observation are included 566 mothers with an average age of 28.8±5.1 years. The youngest woman is 14 years old and the oldest - 46 years old. The predominant age group is 20-29years – 60% (*Table 2.1*).

***PaNJ:** Comparison of mean values of BR of NB according to maternal age at birth by postnatal days are presented in Fig. 2.1. The highest average levels of BR are reported in the NB of mothers under 20 years old, and the lowest levels – in the children of mothers ≥40 years. There was a significant difference in the average levels of BR on the second (p=0.022), third (p=0.016), fourth (p=0.006) and fifth (p=0.055) day in the group of mothers ≤20 years. The coefficient of determination (R^2) for these postnatal days is accordingly 2,6%;2.2%; 3.4%; 3.5%.

***PrNJ:** The average age of the mothers of the group of children with PrNJ is 29.0±5.5 years, and of those whose children had PhNJ is 28.9±5.2 years - the difference is not significant. In the different age groups of mothers a similar share of NB to PhNJ and PrNJ are reported (*Table 2.2*).

In Fig. 2.2. is presented the incidence of NB with HB in percentage during the first five days according to the age of the mother. We prove a significant difference in the incidence of NJ according to the age of the mother (p = 0.001). The group which has the biggest share of HB in NB is the one with mothers aged 20-29 years – 41.30%, and the lowest - in mothers ≥40 years – 20%. The statistical analysis made with the Pearson correlation coefficient (r) showed that there was a statistically significant inversely weak linear relationship between second day BR levels at NB and maternal age (r(362)=-0.112, p=0.033).

2.1.1.2. Marital status

* **PaNJ:** The children included in this study, for the most part – 58.7%, are born to married couples. In 41% of NBs raised in families and in 36.1% of NBs raised by couples who are not married, PaNJ was registered. No correlation was found between BR levels and maternal marital status (*Table 2.1*).

*__PrNJ__: In Group PrNJ the children from families are not significantly more – 68%, compared to Group PhNJ – 55% (r=0.062) (*Table 2.2*). There was no correlation between the marital status of the mother and the presence of PrNJ in the NB

Table. 2.1. Distribution of PaNJ cases according to sibling history of NJ, maternal demographic factors and data from obstetric history ($p \leq 0.05$; r_s - Spearman's rank correlation coefficient, R^2 - coefficient of determination)

Indicator	*Groups*	*N(%)*	*% PaNJ of the group*	*p*	r_s	R^2
Age *28.8±5.1*	<20 gr. 20-29 30-39 ≥40	13 (2) 341 (60) 196 (35) 16 (3)	41 37 20 39	Day 2 – 0. 022 Day 3 – 0.016 Day 4 – 0.006 Day 5 – 0.055		2.6% 2.2% 3.4% 3.5%
Marital status	Married Single Another	332 (59) 230 (40) 4 (1)	41 36 25	NS		
Education (school)	Primary Secondary University	13 (2) 356 (63) 197 (35)	54 35 45	0.036	0.096	
Place of residence	Reg. town Town Village	377 (67) 90 (16) 99 (17)	38 39 41	NS		
Pregnancies (sequence)	1 >1	393 (69) 173 (31)	39 39	NS		
Birth (sequence)	1 >1	407 (72) 159 (28)	39 39			
History for NJ	Total N with NJ	146 102	70	0.025	0.227	

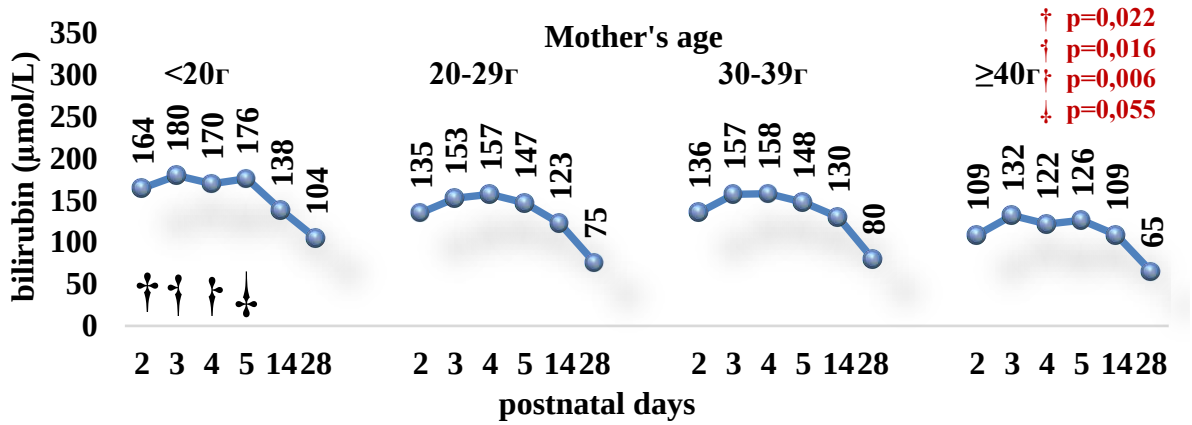

Fig. 2.1. Mean levels of total bilirubin (µmol/L) in the monitored population according to maternal age by postnatal days.

Table. 2.2 Comparative characteristics of the PhNJ and PrNJ groups (PhNJ – physiological neonatal jaundice, PrNJ – prolonged neonatal jaundice, PN-birth by vaginal route, SC – Caesarean Section)

Indicator		PhNJ (%)	PrNJ (%)	P
Gender	♂ ♀	51 49	60 40	0.078
Weeks	Mean. 37-38 39-41	39.0±1.1 38 62	38.5±1.0 53 47	<0.001
Weight (g)	Mean. <3000 3000-3999 ≥4000	3355.1±417.3 22 72 6	3374.4±401.1 22 70 9	NS
Mechanism of birth	PN SC	45 55	46 54	NS
Apgar	≤7 >7	18 8	17 83	NS
Season of birth	Winter Spring Summer Fall	14 31 35 20	22 19 37 23	NS
Mother's age (year)	Mean age <20 20-29 30-39 ≥40	28.9±5.2 1 61 34 4	29.0±5.5 1 63 32 4	NS
Marital status	Married Single	55 45	68 32	0.062
History for NJ	Yes Not	53 47	78% 22%	0.017
Education (school)	Primary Secondary University	2 64 34	1 58 41	NS
Domicile	Reg. town Town Village	66 14 20	70% 10% 20%	NS
Sequence of Pregnancy	1 >1	72 28	60% 40%	NS
Sequence of Birth	1 >1	72 28	65% 35%	NS

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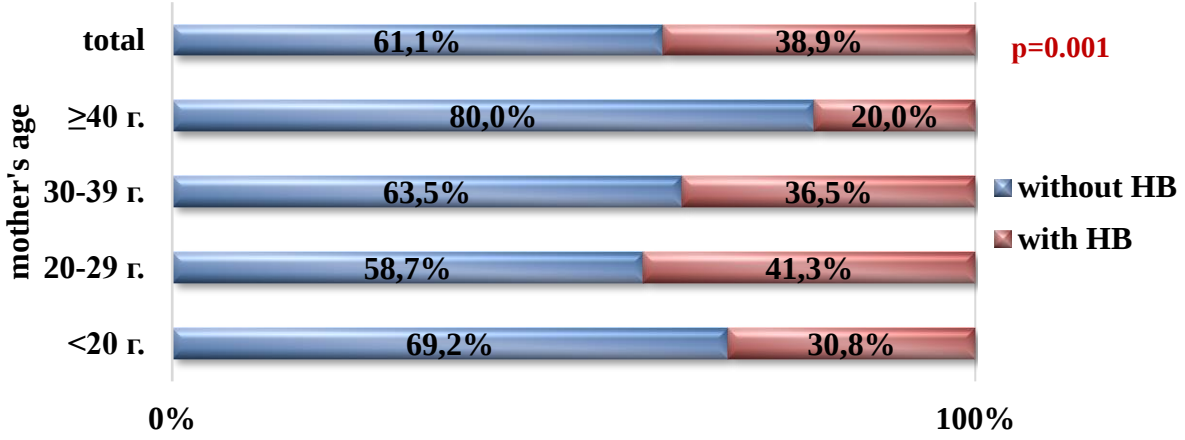

Fig. 2.2. Manifestation of hyperbilirubinemia in newborns (in %) according to the age of the mother.

2.1.1.3. Education

***PaNJ:** The majority of the group of 566 mothers are those with completed secondary school – 63%, with university education are 34% and primary school – 2%. The percentage of children with PaNJ in mothers with primary education is 53.8%, in those with secondary education - 34.8%, and in university - 45.2%. No correlation was found between the level of education of mothers and the incidence of PaNJ in their NB, as well as the mean values of BR (*Table 2.1*).

***PrNJ**: The distribution according to the level of education of the mother in Group PrNJ (1% : 58% : 41%) does not show a significant difference with that in Group PhNJ (2% : 64% : 34%) (*Table 2.2*). There was no connection between the manifestation of PrNJ and the educational level of the mother.

2.1.1.4. Domicile

***PaNJ**: According to the place of residence, the contingent in the observed population is distributed as follows: living in a district town – 66.6%, in a smaller town – 15.9%, in a village – 17.5%. Children with PaNJ in the three groups were 38.2%, 38.9%, 41.4%. No significant difference in mean values of BR depending on residence was demonstrated (*Table 2.1*), and there was no correlation between the levels of BR in the early neonatal period and the place of residence.

***PrNJ:** In Group PrNJ the distribution of NB according to the place of residence is 70% from a district town, 10% from a small town and 20% from a village. Between the PhNJ and PrNJ groups no difference was found in the percentage distribution of NB by place of residence (66% : 14% : 20% respectively). There was no significant difference in the frequency of PrNJ depending on the place of residence. Compared the average levels of BR by place of

residence, at day 14, were unsignificantly higher in children raised in a district city (p = 0.079; Eta²=0.035) (*Fig. 2. 3*).

Multifactorial linear regression analysis of maternal demographics (age, residence, education, marital status) versus postnatal day BR levels in their children showed a significant negative relations between maternal age and BR in NB at day 2 postpartum (R^2,1.3; CI, -1.660÷-0.071, p=0.033). For the other demographic indicators, no significance was reported (*Table 2.3;Fig. 2.4*).

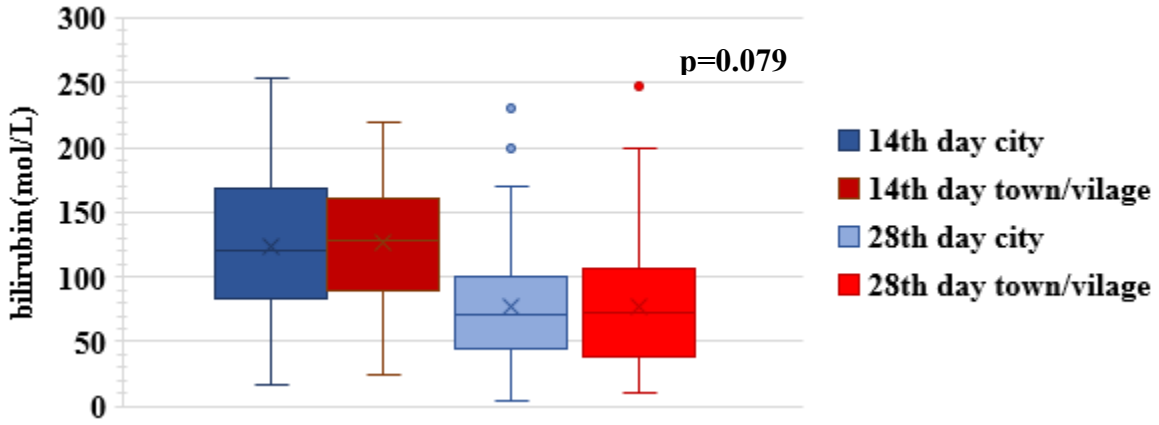

Fig. 2. 3. Transcutaneous bilirubin (µmol/L) levels at days 14th and 28th, distributed according to residence of 92 NB with PrNJ.

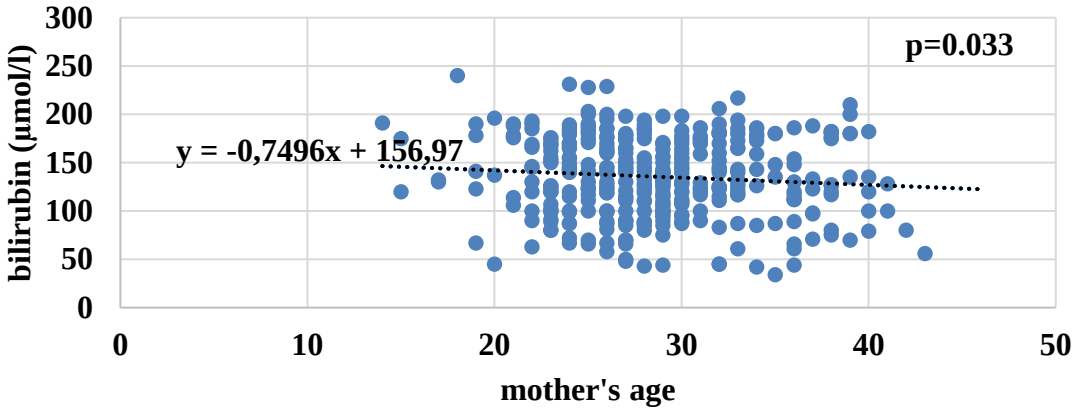

Fig. 2.4. Linear regression analysis – mother's age and newborn's total bilirubin level in second postnatal day.

2.1.3. Pathology of pregnancy

Using Pearson's correlation coefficient, the link between bilirubinemia levels of NB and maternal pregnancy pathology was measured. The data of pregnancy pathology was collected by anamnesis of the mother's pregnancy and epicrises from hospitalizations and

outpatient lists from examinations during pregnancy. A summary of maternal pregnancy morbidity is presented on Table 2.4.

Table 2.3. Maternal demographics factor and manifestation of hyperbilirubinemia in the newborn.

Demographic factors⁂	***P****	***R²***	***CI***
1	0.033	1.3%	-1.660÷-0.071
1, 2	0.097	0.7%	
1, 2, 3	0.064	1.2%	
1, 2, 3, 4	0.118	0.9%	

**r≤0.05; ⁂ 1 – age of the mother; 2 – marital status; 3 – place of residence; 4 – education*

Table. 2.4. Maternal diseases during pregnancy (R²-coefficient of determination).

Maternal pathology	***n (% of all NRs)***	***% NR s HB from accordingly maternal disease***	***P**** ***(for a level of BR)***	***R²***
Obezitas	81 (14.3%)	38.3	NS	
Threatened premature birth	29 (5.1%)	34.6	Day 2 – 0.029 Day 3 – 0.025	1.3% 1.1%
Thyroid	41 (7.2%)	39.0	NS	
Preeclampsia	48 (8.5%)	33.3	NS	
Thrombophilia	13 (2.3%)	23.1	Day 14– 0.008	
Anemia	27 (4.8%)	37.0	NS	
Infections	56 (9.9%)	48.2	NS	
Diabetes	2 (0.3%)	100.0	Day 4 – 0.002 Day 5 – 0.001	

**p≤0.05*

2.1.3.1. Threatening premature birth

***PaNJ:** Pathology of pregnancy with threatening premature birth and clinic of bleeding requiring hospital treatment is registered in 5.1% of mothers (Table 2.5). The incidence of HB in NB from these mothers was 34.6%. The mean values of BR in NB of these mothers are significantly higher on the second (156.1±39.7 μmol/L) and third (174.2±47.6 μmol/L) postnatal day compared to the other groups. The correlation between HB in NB and threatening preterm birth was slightly positive (second day: r(360)=0.115, p=0.029; third day: r(468)=0.103, p=0.025). The uncertainty coefficient R is 1.3% and 1.1% respectively (*Table 2.4; Table 2.5; Table 2.6*).

***PrNJ:** History of pathology with threatening premature birth does not affect the levels of BR at the end of the neonatal period. There was no connection between this parameter and the PrNJ of the NB

Table. 2.5. Average levels of BR of NB(μmol/L) according to the pathology of maternal pregnancy (FRS – female reproductive system; URT – upper respiratory tract p=0.029; † p=0.025; ⸸ r=0.020;).*

Maternal pathology	***Values of total BR by postnatal days***						
	Day 1	***Day 2***	***Day 3***	***Day 4***	***Day 5***	***Day 14***	***Day 28***
Obezitas	**90.5± 32.4**	**138.3 ± 40.1**	**153.0 ±-37.3**	**158.6 ±37.3**	**141.1 ±30.0**	**127.6 ±58.8**	**80.5 ±50.0**
Threatened prem. birth	**111.3 ±30.8**	**156.1 ±39.7***	**174.2 ±47.6†**	**170.2 ±32.8**	**147.3 ±43.5**	**128.2 ± 2.7**	**87.3 ±58.1**
Pre-eclampsia	**86.3 ±31.6**	**137.2 ±42.0**	**153.1 ±38.1**	**156.1 ±26.9**	**138.0 ±24.9**	**116.4 ±47.9**	**68.5 ±43.4**
Thrombo-philia	**97.4 ±25.7**	**142.6 ±34.4**	**154.5 ±17.0**	**154.9 ±44.5**	**137.4 ±39.2**	**85.3 ±31.7⸸**	**45.0 ±30.6**
Anemia	**97.4 ±25.7**	**142.6 ±34.4**	**154.5 ±17.0**	**154.9 ±44.5**	**137.4 ±39.2**	**85.3 ±31.7**	**51.7 ±21.8**
Infections	**99.2 ±32.0**	**137.1 ±40.5**	**151.9 ±38.8**	**156.5 ±32.6**	**153.3 ±31.1**	**117.9 ±46.7**	**77.6 ±45.6**

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2.1.3.2. Overweight during pregnancy

With registered overweight in the abdomen are 81 (14.3%) of the women who have recently given birth, and 31 (38.3% of the women with obesity) of their NB are found HB. There was no association with this pathology of pregnancy and manifestation of PaNJ and PrNJ in NB. No higher levels of BR were recorded in this NB group for the whole neonatal period (*Table. 2.4; Table. 2.5; Table. 2.6*).

2.1.3.3. Preeclampsia

*** PaNJ:** The mothers who had hypertension or preeclampsia during pregnancy were 8.5% of the group. In their children, 33.3% had HB, which is less than the average incidence of HB in the monitored population. The mean levels of BR during the early neonatal period in children of women who have recently given birth with Preeclampsia/Hypertension are lower than those of children whose mothers had other patology during pregnancy. The correlational analysis between BR levels in NB and Preeclampsia/Maternal hypertension showed no association between them during the early neonatal period.

***PrNJ:** In the prolonged forms of NJ, was found a minor correlation with this pathology of maternal pregnancy (r=0.091, p=0.045 – for the 14th day, r=0.121, p=0.021 – for the 28th day) (*Table 2.4; Table 2.5; Table 2.6*).

*Table. 2.6. Correlation between maternal diseases during pregnancy and bilirubin of newbotn (r–Pearson coefficient;*p≤0.05)*

Day		*Obezitas*	*Threatened prem. birth*	*Thyroid gland*	*Pre-eclampsia*	*Thrombo-philia*	*Anemia*	*Infections*
1	*p*	**0.056**	**0.103**	**0.027***	**0.386**	**0.471**	**0.119**	**0.904**
	r	**-0.117**	**0.093**	**-0.140**	**0.021**	**-0.005**	**0.086**	**0.009**
2	*p*	**0.311**	**0.014***	**0.413**	**0.237**	**0.304**	**0.355**	**0.799**
	r	**0.026**	**0.115**	**0.012**	**0.038**	**0.027**	**0.020**	**0.013**
3	*p*	**0.428**	**0.013***	**0.393**	**0.443**	**0.496**	**0.027***	**0.627**
	r	**-0.008**	**0.103**	**-0.013**	**0.007**	**0.000**	**-0.089**	**-0.022**
4	*p*	**0.363**	**0.037***	**0.423**	**0.327**	**0.416**	**0.370**	**0.895**
	r	**0.018**	**0.094**	**-0.010**	**0.024**	**-0.011**	**0.017**	**-0.007**
5	*p*	**0.114**	**0.500**	**0.073**	**0.499**	**0.196**	**0.051***	**0.380**
	r	**-0.083**	**0.000**	**-0.100**	**0.000**	**-0.059**	**-0.112**	**0.060**
14	*p*	**0.339**	**0.402**	**0.138**	**0.045***	**0.010***	**0.106**	**0.346**
	r	**0.022**	**0.013**	**-0.059**	**0.091**	**-0.126**	**0.067**	**-0.050**
28	*P*	**0.287**	**0.207**	**0.114**	**0.021***	**0.062**	**0.195**	**0.172**
	r	**0.034**	**0.049**	**-0.072**	**0.121**	**-0.092**	**0.051***	**-0.081**

**p≤0.05*

2.1.3.4. Pathology of the thyroid gland

***PaNJ:** Thyroid pathology (Hypothyroidism, Hashimoto's Thyroiditis, Goiter) requiring thyroid hormone treatment occurs in 41 (7.2%) of the mothers (*Table 2.4; Table 2.5*). Children with HB from those mothers are 16 (39% from this group). Using the correlation coefficient of Pearson, on day one was found a relation between bilirubinemia and the presence of thyroid pathology in the mother. A statistically important slightly negative linear relation between the two indicators was found (r=-0.140, p=0.027). The uncertainty coefficient R^2 for these is 2% (*Table 2.4; Table 2.5; Table 2.6*).

***PrNJ:** No correlation was found between thyroid pathology of the mother and developed PrNJ.

2.1.3.5. Thrombophilia

*** PaNJ:** Mothers with thrombophilia are 13(2.3% of the group), and in 3 (23.3% of them) had a child with HB – a significantly lower proportion than average. There was no significant difference in the levels of BR in their children and other NB during the early neonatal period.

***PrNJ:** Significantly lower levels of BR were recorded on the 14th postnatal day (p=0.008) in the NB of mothers with thrombophilia. The mean levels of BR in children of healthy mothers were 126.2±49.4 μmol/L, and in the group with thrombophilia were 85.2±31.7 μmol/L. The correlation analysis showed a significant negative relation for the levels of BR on that day (r=-0.126, p= 0.010) and the coefficient of determination was R^2=1.6% (*Table 2.4; Table 2.5; Table. 2.6*).

2.1.3.6. Pregnancy anaemia

*** PaNJ:** Anemic conditions that required therapy during pregnancy with iron-containing drug were recorded in 27 (4.8% of women), and in 10 (37% of those anemic mothers) have children with HB. A weak negative correlation was observed between maternal anemic states during pregnancy and HB in NB during the early neonatal period (r=-0.089, p=0.027 on day three; r=-0.112, p=0.051 on day 5), with R^2=1.3% on day five (*Table 2.4; Table 2.5; Table 2.7*).

***PrNJ:** On day 14th and 28th, the average BR values of NB of this group are lower than average. Pregnancy anemia had weak correlation with BR levels at day 28 in NB with PrNJ (r=0.195; p=0.051).

2.1.3.7. Inflammatory diseases during pregnancy

During pregnancy, in 56 of the mothers (9.9%) had inflammatory diseases (infections of the female reproductive system, urinary system and upper respiratory tract) that required systematic and local antibiotic and / or antifungal treatment. No difference was found in the levels of BR in the NB of these mothers compared with the other children for the whole neonatal period (*Table 2.4; Table 2.5; Table 2.6*).

The differentiation of maternal inflammatory diseases by systems correlated with the incidence of neonatal HB. Registered inflammatory diseases of the urinary system with a proven microbiological causative agent (asymptomatic bacteriuria, acute cystitis, acute pyelonephritis, hydronephrosis with significant bacteriuria) during pregnancy occurs in 16 (2.8%) of mothers, of which 48.1% had newborn with HB in the first 5 days. There was no difference in the levels of BR in these NB compared to the other children. Inflammatory diseases of the female reproductive system (FRS) during pregnancy (bacterial vulvovaginitis,

microbiological colonization of the vagina, chorioamnionitis) were registered in 17 (3%) of the cases, and in 10(58.8%)NB of them had HBB, which was significantly higher level of bilirubin on the third postnatal day 171.5±33.7 μmol/L (p=0.023). Correlation analysis demonstrated a weak positive association on the third day between diseases of the FRS and HB in the NB (r=0.114, p=0.007). The correlation coefficient is 1.3%. During childbirth, 25 (4.5%) of the mothers had inflammatory diseases of the respiratory system and were treated with systematic antibiotic. In the early neonatal period, the BR levels of their children did not differ from those of the general population. On day 28th, the values of BR that were registered were significantly lower than the average – 49.4±37.8 μmol/L (p=0.038). With the applied correlation analysis, a weak negative relationship was found between the levels of BR on postnatal day 28th and the respiratory tract morbidity in the mother (r=-0.120, p=0.022) and the coefficient R^2=1.4%.

2.1.3.8. Diabetes of the pregnant woman

In the observed group, there were only two children born to mothers with diabetes who had a clinic of diabetic fetopathy. In one of those newborns, an early HB appeared, which subsequently passed into PrNJ.

2.1.3.9. Sequence of pregnancy

*** PaNJ:** Children who are born from first pregnancy are 396 - 70% of the observed. No significant difference in bilirubinemia by days was found (*Fig. 2.5*) depending on the sequence of pregnancy. There was no correlation between PaNJ and the sequence of pregnancy. NB with HB, born from first pregnancy and needing phototherapy, were 45.3%, and from second or consecutive pregnancy – 50.9%. The difference is not significant.

***PrNJ:** No significant difference in the incidence of PrNJ was reported according to the number of pregnancies. There is also no difference in BR levels at the end of the neonatal eriod according to this indicator.

2.1.3.10. Sequence of birth

***PaNJ:** In the monitored population 407 - 71.9% of the NB from first birth and 28.1% from second or subsequent birth had PaNJ. NB from first compared to those from second or consecutive birth had significantly lower levels of BR on the fourth postnatal day (first birth – 155.30±33.0 μmol/L, second birth – 163.7±30.9 μmol/L) (p=0.037) (*Fig. 2.6*). The percentage needing phototherapy did not differ – 46.2% in those born from first birth, 49.1% – from the second or consecutive birth.

***PrNJ:** No significant difference in the frequency of PrNJ was proven according to the order of birth. For Group PrNJ, there was no difference in bilirubinemia on the 28th day according to this indicator.

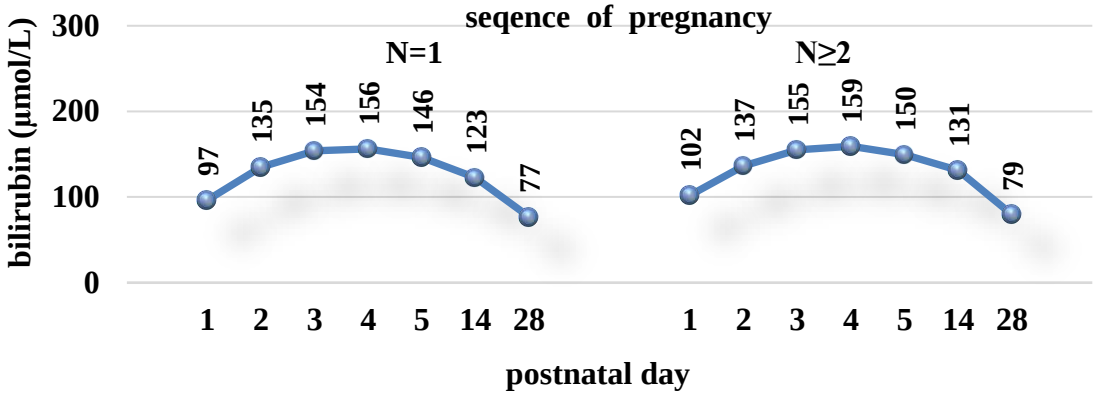

Fig. 2.5. Bilirubin values (µmol/L) according to the order of pregnancy of the mother

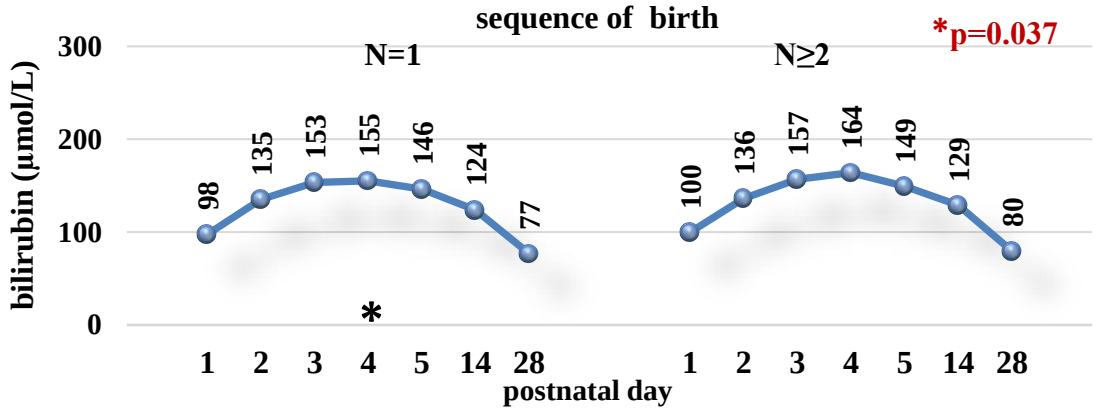

Fig. 2.6. Bilirubin values (µmol/L) according to maternal birth sequence

A linear regression analysis was conducted to assess the influence of the presence of pregnancy pathology on HB during the first five days, which reported a significant relationship between the levels of BR on the second (F=4.828, p=0.029) and third day (F=5.046, p=0.025) and threatening preterm birth, with a corrected coefficient of determination R^2 respectively 1.3% and 1.1% (*Fig. 2.7A and Fig. 2.7B*).

The multiple linear regression from the variables "threatening preterm birth" and "maternal FRS diseases" on the level of BR on day three was statistically significant - F=5.94, p=0.003. The value of the corrected coefficient of determination R^2 is 2.1%, indicating a weak dependence. The combination of the variables "inflammatory diseases of the FRS" and "of

excretory system" for the level of BR on the third day is also statistically significant – F = 3.024, p = 0.05. Coefficient of determination - R^2=1.3%.

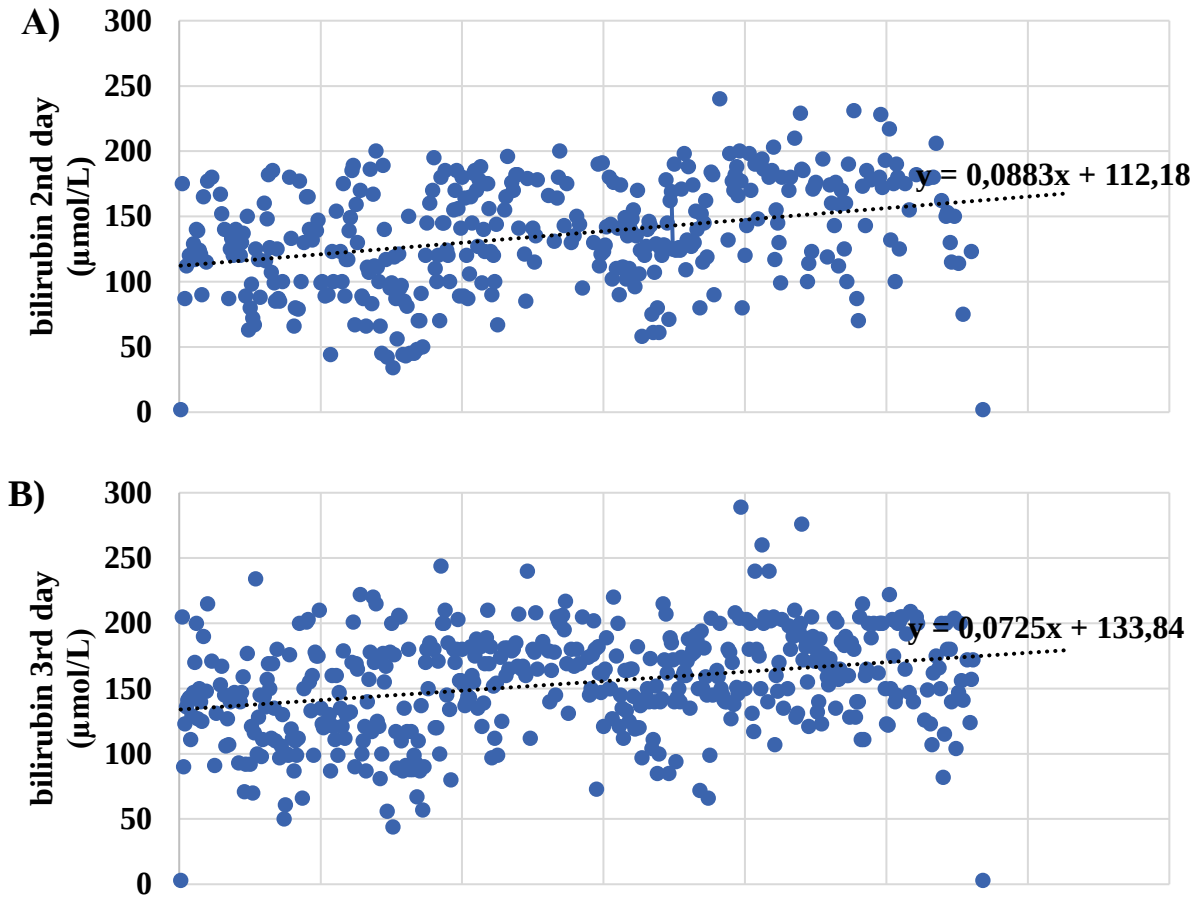

Fig. 2.7. Linear regression analysis – pathology of pregnancy with threatening premature birth and level of total bilirubin in newborns on day two (A) and third day (B).

Table. 2.7. Multiple linear regression between newborn bilirubin level on postnatal day 3 and maternal pregnancy pathology.

Diseases	***F***	***p***	***R²***
Total for all registered Diseases during pregnancy	**5.046**	**0.025**	**3.5%**
Threatening prematute birth & FRS	**5.96**	**0.003**	**2.1%**
FRS & Excretory system	**3.024**	**0.050**	**1.3%**
Prematute birth & Anemia & Preeclampsia	**2.844**	**0.037**	**1.8%**
Prematute birth &Thyroid gland & FRS &Preeclampsia & Anemia	**2.417**	**0.019**	**3.5%**

A multiple linear regression between the combination of factors "threatening preterm birth", "pregnancy anemia" and "preeclampsia" showed a statistically significant influence relative to the level of third day BR – F=2.844, p=0.037 and R^2=1.8%.

The combination of factors of pregnancy pathology: threatening premature birth, thyroid pathology, inflammatory diseases of excretory system and FRS, preeclampsia and anemia of pregnancy by using multiple linear regression showed that significantly determines the level of BP on the third postnatal day – F = 2.417, p = 0.019. The corrected coefficient of determination is R^2=3.5% (*Table 2.7*).

2.2. Obstetric factors

2.2.1. Mechanism of childbirth

***PaNJ:** The children born by normal mechanism (PN) in the observed group were 246(43.1%), by surgical route (SC) - 56.5%, in two NB the birth was carried out with instrumental intervention. From 1st to 5th postnatal day in children born vaginally, HB occurs in 19%, 25%, 21%, 10% and 10%, respectively. In those born by SC for the same period, the incidence of HB was 13%, 17%, 12%, 5%, 5%, respectively. NB born by PN compared to those born by SC had a significantly higher frequency of HB for the first 5 days (1st day p=0.020, 2nd day p=0.014, 3rd day p=0.002, 4th day p=0.015, 5th day p=0.015) (*Fig. 2.8A*). When comparing the incidence of HB on postnatal days between those born by SC and born by PN with applied stimulation with less than 5E oxytocin or non-administered oxytocin, no difference was found.

The bilirubinemia levels in NB by PN on the second postnatal day were 141.5±39.6 μmol/L, on day three – 158.6±37.3 μmol/L, and in the SC-born 131.1±40.6μmol/L and 151.3±39.7 μmol/L (p=0.015; p=0.044).

In newborns, by born vaginally, we compared the mean levels of BR in children who were given Oxytocin stimulation with more than 5E and those who were not given stimulation or were applied below 5E Oxytocin. Children with more than 5E Oxytocin were 31 (12.6% of PN). We found a significant difference between the two groups from the first to the fifth postnatal day (p=0.009, p<0.001, p<0.001, p=0.001, p=0.021). In the first group, the BR levels were 119.9±27.5 μmol/L, 180.2±30.8 μmol/L, 200.35±23.5 μmol/L, 175.8±20.2 μmol/L, 161.0±21.9 μmol/L. In the second group, the BR from the first to the fifth day had the following levels: 97.6±28.6 μmol/L, 133.3±36.6 μmol/L, 151.0±34.2 μmol/L, 154.6±35 μmol/L, 146.1±34.8 μmol/L. We found a moderately strong correlation between the mechanism of birth by the vaginal route with the administration of larger doses of 5E oxytocin and BR levels during the early neonatal period (p=0.001; r=0.246).

Compared the mean levels of BR from the first to the fifth postnatal day of children born by surgical means and of children born vaginaly with oxytocin below 5E/withought Oxytocin did not show a significant difference (*Fig. 2.8 B*).

***PrNJ:** Also a significant difference in the BR levels was found depending on the mechanism of birth on the 14th postnatal day (PN – 134.1±51.7 µmol/L; SC – 119.0±47.2 µmol/L; p=0.005) and by day 28 (PN – 85.6±45.3 µmol/L; SC – 72.4±45.3 µmol/L; r=0.017) (*Fig. 2.9A*). No difference was found in mean levels of BR in those born by surgical route and those born by normal mechanism with less than 5E administered Oxytocin (*Fig. 2.9.B*).

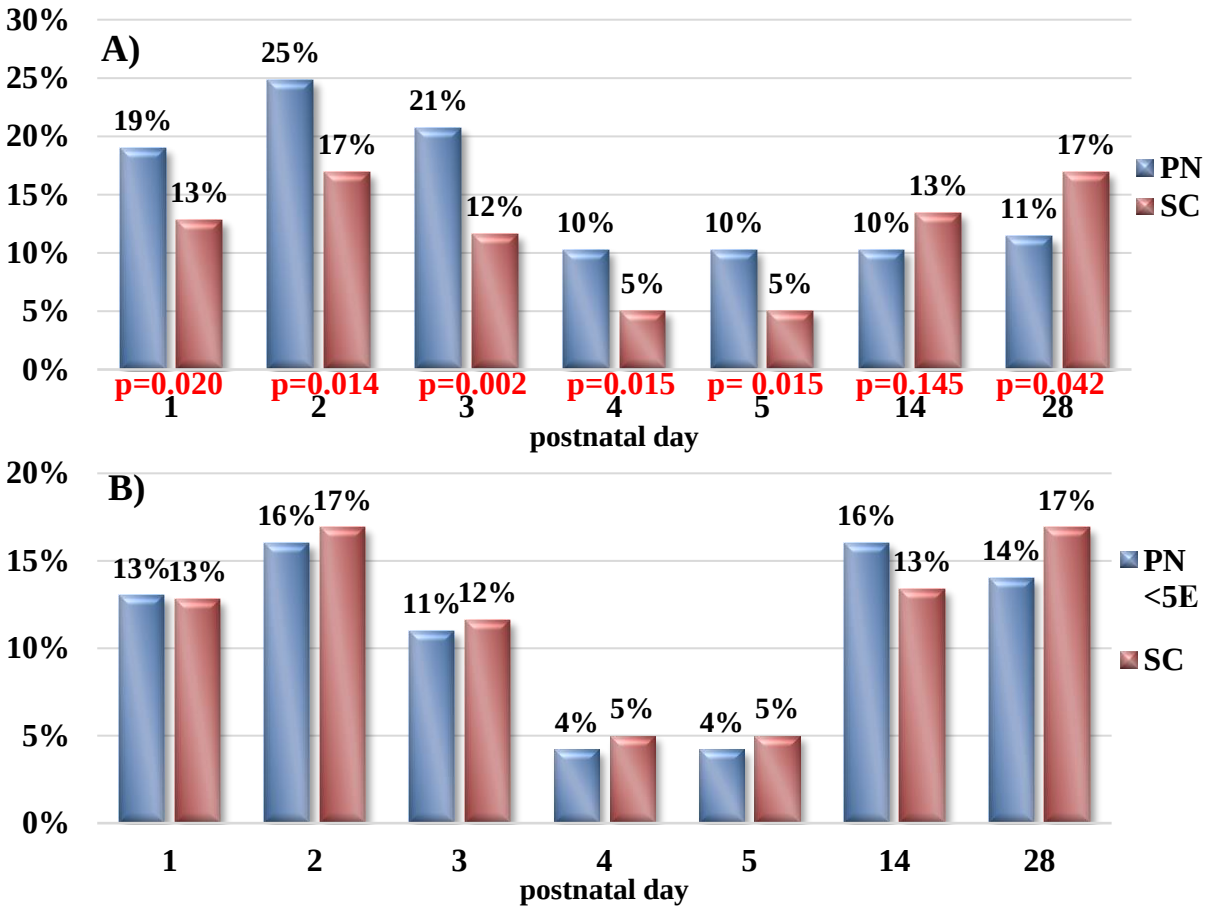

Fig. 2.8. Incidence of HB (in %) according to the mechanism of childbirth, distributed by postnatal days: A) Comparison between PN and SC births; B) Comparison between PN births with less than 5E Oxytocin administered or no Oxytocin and SC.

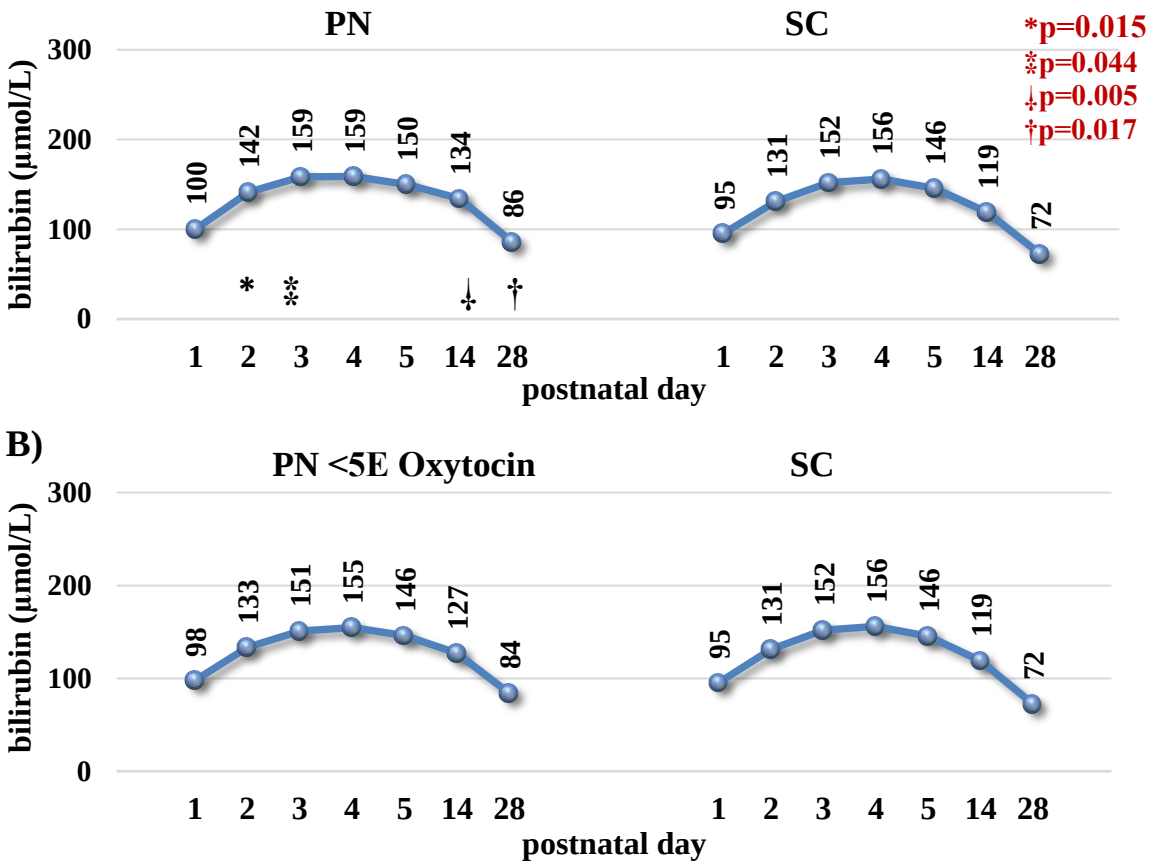

Fig. 2.9. Total bilirubin levels (µmol/L) depending on birth mechanism by postnatal days : A) Comparison of mean bilirubin levels between PN and SC births; C) Comparison of mean bilirubin levels between PN births with less than 5U Oxytocin administered or no Oxytocin and SC births.

2.2.2. Season of birth

***PaNJ:** The measured mean levels of BR by postnatal days of the children depending on the season of birth are presented in Fig. 2.10.

When comparing mean BR levels we found a significant difference depending on the birth season for the period between 2nd and 5th postnatal day (*Table 2.8*). Children born in summer have the highest average levels of BR, followed by those born in spring. The newborns who have the lowest values of BR are those born in the autumn. By the 14th and 28th day, the highest levels have those born in the spring, and for the 28th day this difference is significant (*Fig. 2.10; Fig 2.11*).

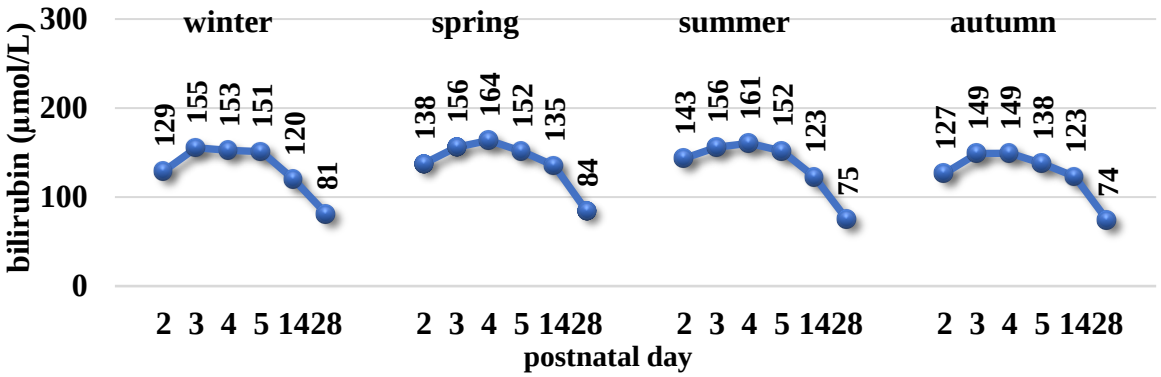

Fig. 2.10. Mean levels of total bilirubin in newborns in the observed population according to postnatal birth season

The coefficient of determination (R^2) of the season of birth was 4.0% on the first day, 2.9% on the second, 0.6% on the third, 3.1% on the fourth and 4.0% on the 5th day. By the 14th day it was 1.3%, and at the end of the neonatal period – only 0.9%.

Table 2.8. Difference (p) in bilirubin levels in the observed population according to season of birth for 2nd to 5th postnatal day (T-test).

Season	***Winter***	***Spring***	***Summer***	***Autumn***
Winter		**Day 4 / p=0.044**	**Day 2 / p=0.023**	**Day 5 / p=0.040**
Spring	**Day 4 /p=0.044**			**Day 1 / p=0.004** **Day 4 / p=0.001** **Day 5 / p=0.018**
Summer	**Day 2 / p=0.023**			**Day 2 / p=0.003** **Day 4 / p=0.012** **Day 5 / p=0.009**
Autumn	**Day 5 / p=0.040**	**Day 1 / p=0.004** **Day 4 / p=0.001** **Day 5 / p=0.018**	**Day 2 / p=0.003** **Day 4 / p=0.012** **Day 5 / p=0.009**	

***PrNJ:** In the group of NBs with PrNJ, the highest number of children were born in summer – 37%, followed by those in autumn – 23%, winter – 22% and the lowest number in spring – 19% (r<0.001) (*Table 2.2*). On day 28, a statistically significant difference was reported, F(3,89)=3.727, p=0.014 for the mean levels of BR according to the season of birth(*Fig. 2.11*). The magnitude of the effect is Eta^2=0.336, which is a typical size. A Tuki HDS (Tukey) posthoc test was used, which showed that there was a statistically significant difference between the mean levels of BR of those born in summer (155.4±31.8 µmol/L) and autumn (134.4±19.9 µmol/L) (p=0.018). In the duration of appearance of PrNJ according to the season

of birth, a statistically significant difference F(3,89)=3.982, p=0.010 was also found. The magnitude of the effect is Eta²=0.346, which is greater than the typical one. With Tukey's posthoc test was found that the longest is the icterus of those born in summer (64.7±15.2 days) and there is a statistically significant difference with those born in winter (53.8±11.1 days, p=0.018) and autumn (55.0±10.5 days, p=0.008) (*Fig. 2.11)*

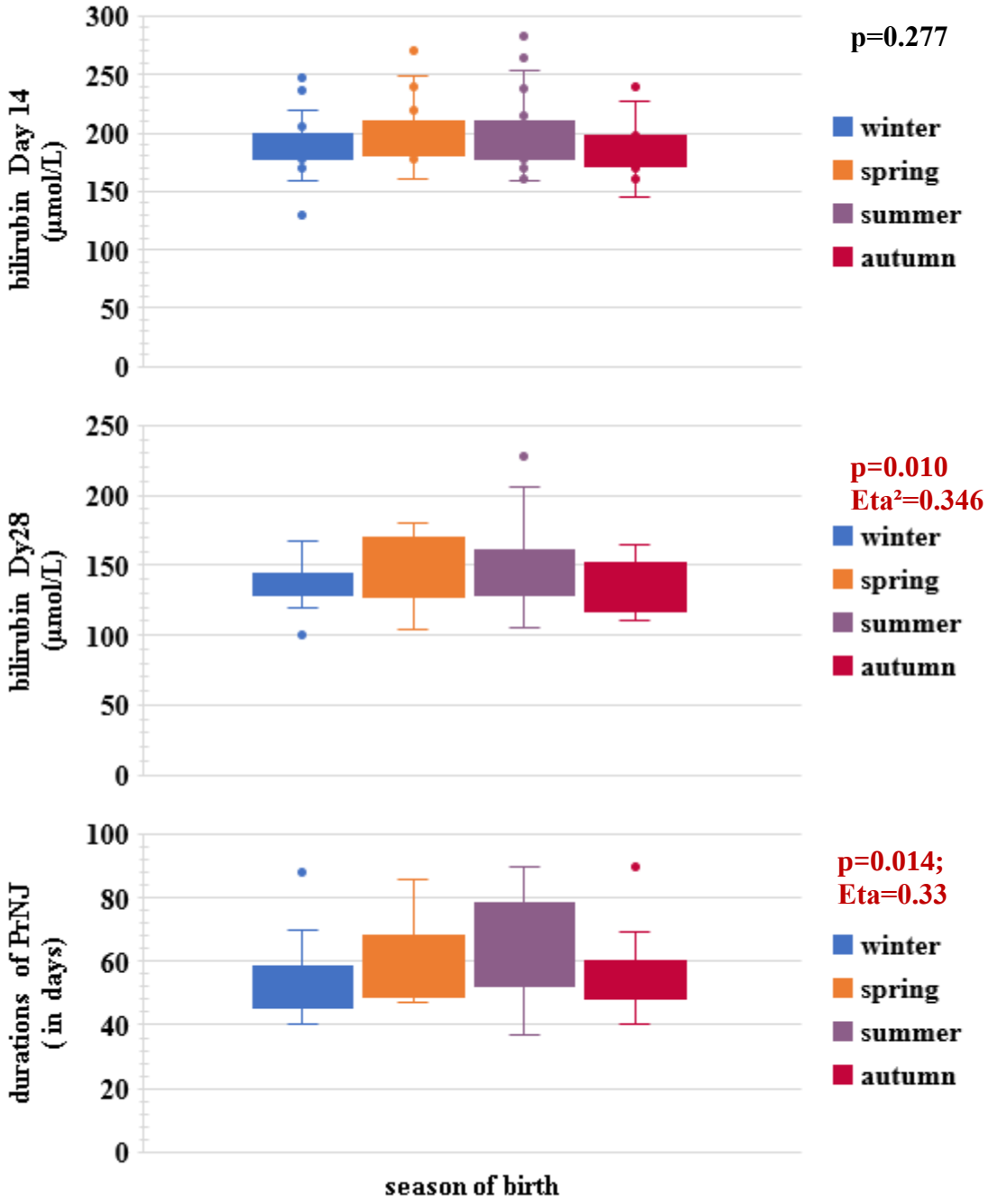

Fig. 2.11. Transcutaneous bilirubin (µmol/L) levels on day 14 and 28 and duration of PrNJ manifestation, distributed according to the season of birth at 92 HP with PrNJ.

2.3. Neonatal factors:

2.3.1. History of NJ in older siblings

***PaNJ:** The mothers who have given birth more than once in the cohort are 152, of which 146 have answered a question whether they have a memory of a developed NJ with the need for therapy in a previous child. A positive answer to this question was given by 66.9%. Newborns, whose older siblings had NJ, had higher mean levels of NJ over the entire neonatal period. In order to investigate the association between the history of NJ in sibling and the presence of HB in a subsequent NB, the rank correlation coefficient Spearman (r_s) was used. Spearman's coefficient is $r_s(98)=0.227$, p=0.025. The magnitude of the effect is close to average. The value of the coefficient of determination R^2 indicates that approximately 5% of the variance of HB is associated with a history of NJ in an older sibling.

On the second postnatal day, the mean level of the BR was 119±36.9 μmol/L in the group without history of NJ and 140.8±40.9 μmol/L in the group with positive history (p=0.020), respectively, (*Fig. 2.12*). In NB with preceding sibling with NJ in 59.8% of the cases was necessary to conduct PhT, while in the other group - only in 29.5%. The Spearman correlation coefficient for relationship between administered PhT and sibling history was rs(144)=0.278, p=0.001. The magnitude of the effect is close to the average. The coefficient of determination is R^2=8%.

***PrNJ**: In the group with PrNJ the share of NB whose older brothers or sisters had PaNJ is significantly higher – 78% (p=0.017), compared to this share in the group with **PhNJ** – 53% (*Table 2.2*).

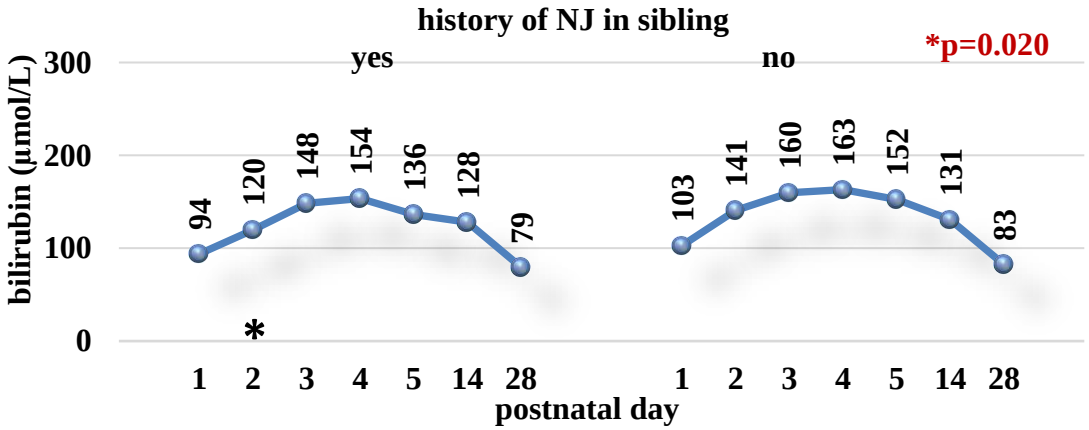

Fig. 2.12. Total bilirubin (μmol/L) values depending on a history of NJ in previous sibling

Multifactorial linear regression analysis between BR levels of NB and pregnancy sequence, birth order and history of HB in previous siblings showed significant values on second (R^2= 8.9%; p=0.032) and fourth postnatal day (R^2=8.2%; p=0.040). A positive history

of HB on the first (p=0.046) and second (p=0.036) day was of independent importance. No correlation was found for the prolonged forms of HB when studying those three indicators (*Table 2.9*).

Table 2.9. Sequence of pregnancy and childbirth and history of HB in sibling and manifestation of NJ on postnatal days – multifactorial linear regression analysis

Day	***Indicators⁂***	***P****	***R²***	***SD***
Day 1		**NS**		
Day 2	**1**	**0.605**	**0.3%**	
	1,2	**0.290**	**2.6%**	
	1,2,3	**0.032***	**8.9%**	**5.122÷41.144**
Day 3		**NS**		
Day 4	**1**	**0.037***	**4.3%**	**-32.821÷-1.048**
	1,2	**0.066**	**5.4%**	
	1,2,3	**0.040***	**8.2%**	
Day 5, 14, 28		**NS**		

**r≤0.05*
⁂ 1 – sequence of pregnancy, 2 – sequence of childbirth, 3 – sibling with HB

2.3.2. Gender

***PaNJ**: The gender distribution in the observed group was 48.4%: 51.6% in favor of the boys. In Fig 2.13. a gender distribution according to the type and duration of expression of NJ is presented. In the early neonatal period, there were more girls without NJ – 57.9%, while on day 28 there was no difference between genders. In Group PhNJ and PaNJ, male sex prevails – 54.5% and 51.8%, respectively.

***PrNJ:** In Group PrNJ the share of boys is even higher – 58.5%. No statistically significant difference in the distribution by sex and expression of NJ was demonstrated for the whole neonatal period (p=0.094) (*Fig. 2.13.*). Although there was a difference in the ratio of boys: girls between the groups without prominent NJ (42.1%: 57.9%) and PrNJ (58.5%: 41.5%), it was not significant (p=0.078).

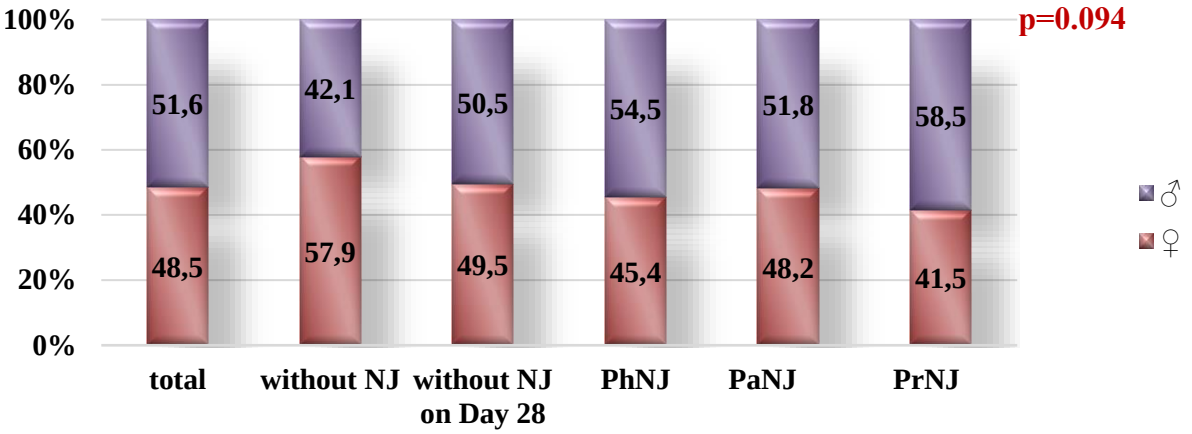

Fig. 2.13. Sex distribution of neonatal jaundice by species (in %).

In Figure 2.14. the dynamics of the mean values of total BR by postnatal days according to the gender of the NB is presented. In boys, higher average levels of total BR from day 1 to day 14 were found, but the difference between the two sexes was not significant for the entire neonatal period.

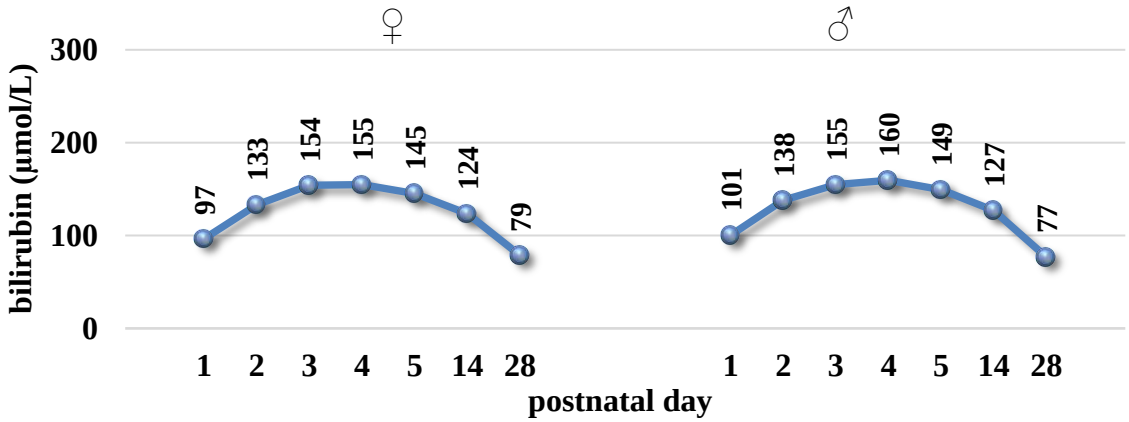

Fig.2.14. Mean bilirubin values in boys and girls (µmol/L) during the neonatal period.

2.3.3. Gestational age

***PaNJ:** The covered group of NBs showed the following distribution by gestational age: 37 weeks – 65 (11.5%) NR, 38 weeks– 195 (34.5%) NB, 39 weeks – 138 (24.4%) NB, 40 weeks – 143 (25.3%) NB, 41 weeks – 24 (4.2%) NB, 42 weeks – 1 (0.2%) NB. Comparing the average levels of total BR shows a significant difference between those born at the age of 37 and those born at the w of 38, 39, 40 and 41 weeks. The levels of BR are higher in children born at 37 week of age for the entire follow-up period. For the first postnatal day, such a difference is between those born at 37 and 40 weeks. (p = 0.030). For the second postnatal day,

there is a difference between NB born at least 37 and 38, 39, 40 weeks. (Respectively p = 0.05; p = 0.017; p = 0.025). On the third postnatal day, the significant difference is between the NB at 37 week and all other age groups (r=0.018; p=0.003; p=0.010; p=0.037). Similar differences are recorded on the fourth postnatal day between the NB at 37 week and those at 39 and 40 weeks (r=0.056; p=0.044) (*Fig. 2.15*).

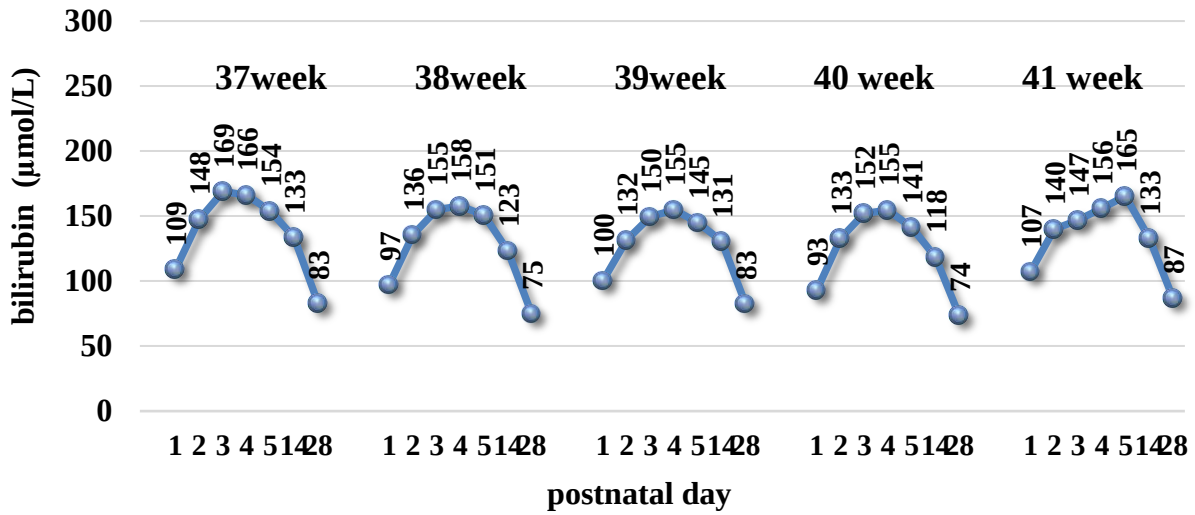

Fig. 2.15. Mean bilirubin levels (µmol/L) depending on weeks at birth.

***PrNJ:** There is no difference in the levels of BR according to the gestational age at delivery by the end of the neonatal period (*Fig. 2.15; Table 2.10*).

Table 2.10. Comparing total bilirubin levels (µmol/L) according to week at birth by postnatal days (T-test).

Day	*Groups by weeks*	*T-test*	*r≤0.05*	*95% CI*
1	**37-40**	**2.230**	**0.030**	**1.578÷30.075**
2	**37-38**	**1.990**	**0.050**	**0.022÷23.839**
	37-39	**2.415**	**0.017**	**2.871÷29.175**
	37-40	**2.280**	**0.025**	**1.925÷27.625**
3	**37-38**	**2.386**	**0.018**	**2.434÷25.537**
	37-39	**3.060**	**0.003**	**6.861÷31.824**
	37-40	**2.623**	**0.010**	**4.161÷29.478**
	37-41	**2.119**	**0.037**	**1.326÷42.838**
4	**37-39**	**1.934**	**0.056**	**0.289÷22.781**
	37-40	**2.036**	**0.044**	**0.289÷22.677**

In order to investigate the relationship between prominent HB and gestational age at birth, Spearman's rank coefficient is used. A weak negative relationship was found for the first

5 days after birth (r=-0.141, p=0.001), for day 14 (r=-0.096, p=0.022) and for day 28 (r=-0.108, p=0.010).

***PrNJ:** For the PrNJ group, a significantly higher share of NB with an age of 37-38 weeks of gestation is reported – 53%, compared to Group PhNJ – 38% (p<0.001).

2.3.4. Birth weight

NBs were divided into three birth weight groups: less than 3,000 grams (21.6% of the children), from 3,000 to 3,999 grams (73.5% of the children) and more than 4,000 grams (4.9% of the children). The group with lowest weight group had the highest levels of BR recorded. The difference with the other groups was not significant, followed for the entire neonatal period (*Fig. 2.16.*).

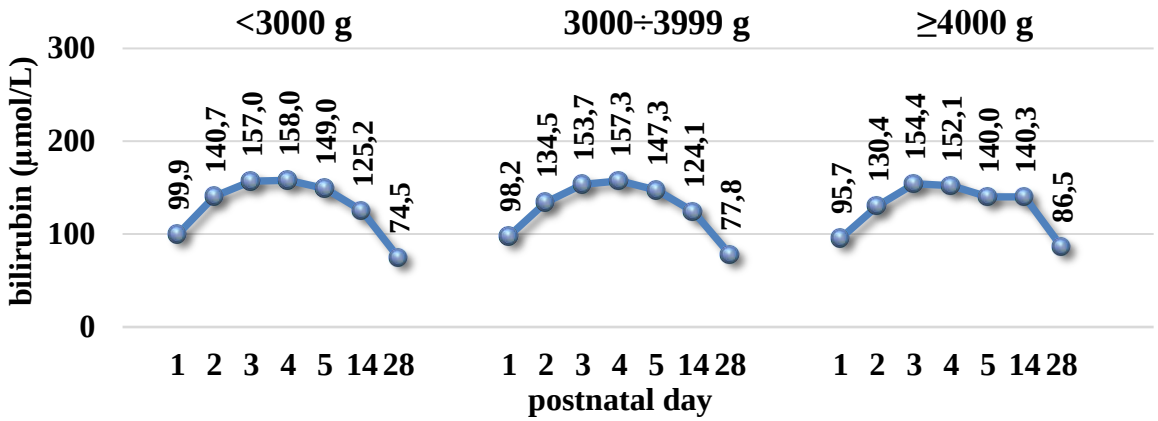

Fig. 2.16. Mean levels of total bilirubin (µmol/L) according to birth weight by postnatal days

2.3.5. Diet

NBs were divided into two groups depending on their diet – exclusively breastfed (234 – 41.3%) and fed with a standard formula for newborns (332 – 58.7%). In the breastfed babies were measured higher mean levels of total BR over the whole observation period and a significant difference was found on the 5th, 14th and 28th days (p=0.04; p<0.001; p=0.001) (*Fig. 2.17*)

***PrNJ:** Exclusively breastfed NBs are the majority in the group with PrNJ - 79%. During the neonatal period, no difference in the levels of BR is recorded depending on the diet in the Group PrNJ. However a significant difference is reported in the BR values measured around the 40th (p = 0.003) and around the 50th day (p = 0.044), and in the exclusively breastfed they are higher (*Fig. 2.18*). There was no significant difference in the duration of the expression of NJ (p = 0.064) according to the feeding method. For breastfed NBs, it is 60±14 days, and for those fed with standard formula – 55±11 days.

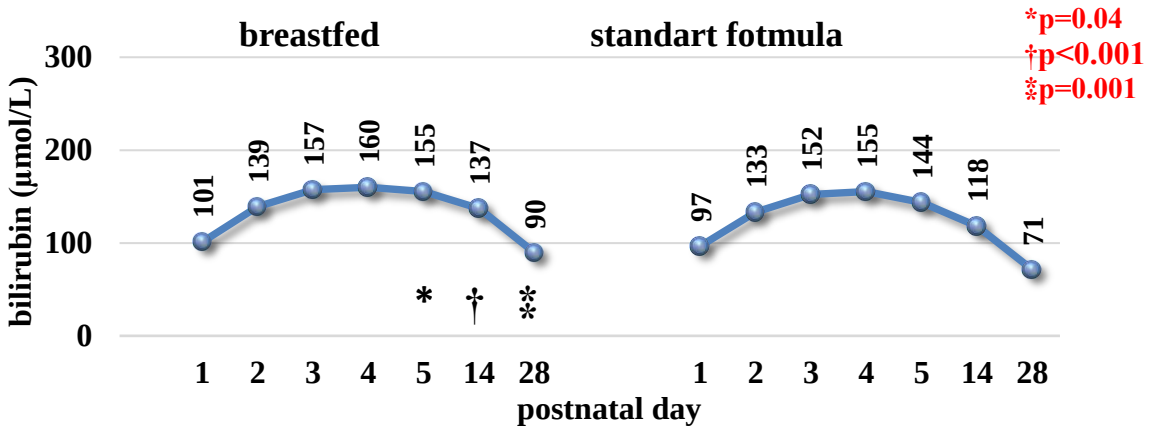

Fig. 2.17. Mean levels of total bilirubin (µmol/L) depending on the diet of newborn by postnatal days

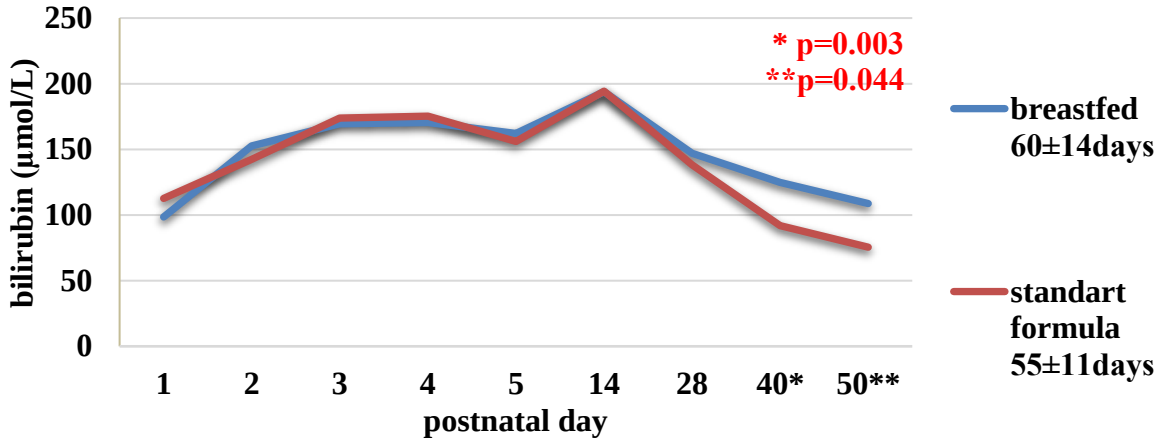

Fig. 2.18. Average bilirubin levels (in µmol/L) according to diet in Group PrNJ

2.3.6. Apgar score

***PaNJ:** On Table 2.11. are shown the average values of total BR according to the Apgar score at 1st and 5th minute. Children born with moderate and severe asphyxia (Apgar score between 4 and 7 on fist minute), had significantly higher mean levels of BR (p=0.001; p=0.011; p=0.039) on first, second and third day. Those born with severe asphyxia (Apgar at 1 min. ≤3) had pathological mean levels of BR for the first days after birth. If the Apgar score is below 8 at the 5th minute, a significant difference in the levels of BR on the first and second day (p = 0.008 and p = 0.006) is registered. Those born with severe and moderate asphyxia (Apgar below 7 at 1st and 5 minutes) on day one been measured mean BR levels above the average for the age.

****PrNJ:*** No correlation was found between PrNJ and Apgar estimate.

Multiple linear regression models were constructed to assess the influence of various factors on the newborn's hyperbilirubinemia: sex, gestational age, birth mechanism, birth weight, Apgar score at 1st and 5th min. (*Table 2.12*). The mechanism of birth significantly affects the levels of bilirubinemia on the second (p = 0.010), third (p = 0.042), 14th (p = 0.009) and 28th day (p = 0.019). The combination of factors mechanism of birth and gestational age at birth, as well as these two factors in combination with birth weight, also play a determining role in hyperbilirubinemia on second (p = 0.005 and p = 0.009), third (p = 0.003 and p = 0.010) and 14th day (p = 0.026 and p = 0.040). In the second model with birth per vias naturales and lower weeks at birth, 2.5% of the cases of hyperbilirubinemia on day 2, 2.4% on day three and 2.1% on day 14 were explained. In a third model, these percentages are 3.2%, 2.4% and 2.4%, respectively. On the first day the low grade on Apgar at 1st minute has a significant independent meaning (p = 0.049) for the level of total bilirubin and explains 2.3% of the case of HB.

Table 2.11. Average values of total bilirubin per day according to Apgar assessment at 1st and 5th minute

Minute of evaluation	***Postnatal day***	***Evaluation by Apgar***	***Total bilirubin (µmol/L)***	***P***
1st	***Day 1***	**1-3** **4-7** **8-10**	**110.3 ± 37.2** **105.6 ± 27.2** **95.7 ± 32.3**	**0.001**
	Day 2	**1-3** **4-7** **8-10**	**148.3 ± 42.6** **143.2 ± 38.8** **132.9 ± 40.7**	**0.011**
	Day 3	**1-3** **4-7** **8-10**	**171.8 ± 27.9** **155.7 ± 39.0** **153.7 ± 38.9**	**0.039**
	Day 4	**1-3** **4-7** **8-10**	**177.5 ± 13.0** **153.8 ± 34.7** **157.8 ± 32.1**	**NS**
	Day 5	**1-3** **4-7** **8-10**	**163.3 ± 33.0** **145.3 ± 33.2** **147.7 ± 30.2**	**NS**
5th	***Day 1***	**4-7** **8-10**	**105.4 ± 29.7** **98.1 ± 31.5**	**0.008**
	Day 2	**4-7** **8-10**	**131.2 ± 38.9** **135.5 ± 40.5**	**0.006**
	Day 3	**4-7** **8-10**	**155.1 ± 47.9** **154.4 ± 38.4**	**NS**
	Day 4	**4-7** **8-10**	**157.1 ± 41.8** **157.2 ± 32.3**	**NS**
	Day 5	**4-7** **8-10**	**151.1 ± 41.3** **147.1 ± 30.5**	**NS**

Table. 2.12. Multiple linear regression for the relation between neonatal and intrapartum factors with total bilirubin levels by age on postnatal days

	Factors*	P**					R^{2}**				
		Postnatal day									
		1	2	3	14	28	1	2	3	14	8
1	1		0.010	0.042	0.009	00.019		1.8%	0.9%	1.9%	.9%
2	1, 2		0.005	0.003	0.026			2.9%	2.4%	2.1%	
3	1, 2, 3		0.009	0.010	0.040			3.2%	2.4%	2.4%	
4	1, 2, 3, 4		0.015	0.023				3.4%	2.4%		
5	1, 2, 3, 4, 5		0.004	0.030				4.6%	2.6%		
6	1, 2, 3, 4, 5, 6		0.009	0.055				4,6%	2.6%		
7	5	0.049					2.3%				

** 1 – mechanism of birth, 2 – weeks, 3 – weight, 4 – sex, 5 – Apgar 1st min., 6 – Apgar 5th min.; ** r≤0.05м; ⁑R^2 – coefficient of determination*

On Table. 2.13 the influence of the studied factors on the manifestation of PaNJ and PrNJ is presented.

Conclusion

According to our data, the prenatal factors that increase the incidence of NJ and serum BR levels in NB are birth sequence, history of jaundice in older siblings, younger maternal age. Inflammatory diseases of the female reproductive system increase bilirubinemia in NB, and pathology of the urinary system - its frequency. If the function of the thyroid gland is well controlled, as well as the balanced iron supplementation of the pregnant, the degree of bilirubinemia is not affected. Preeclampsia and hypertension during pregnancy have a preventive effect on HB in full-term newborns. In exclusively breastfed newborns, PrNJ is more common. NJ is a specific condition for the neonatal period of multifactorial etiology. The combination of various factors – vaginal birth, younger gestation age, lower weight, asphyxia, younger age of the mother, pathology of pregnancy (threatening premature birth, infections of the reproductive or excretory systems), exclusively breastfeeding, is a precondition for the manifestation of HB in NB.

Table 2.13. Relation of the different factors on the manifestation of PaNJ and PrNJ (↑ - increases BR, ↓ - decreases BR)

Factors /	***PaNJ***	***PrNJ***
Mother's age <20 years	↑	
Sequence of pregnancy		
Sequence of birth	↑	↑
Sibling history of NJ experience	↑	
Pathology with threatening yarn. birth	↑	
Pathology of the thyroid gland of a mother	↓	
Preeclampsia / Hypertension		↑
Thrombophilia		↓
Anemia of pregnancy	↓	
Infections of the female reproductive system	↑	
Infections of the urinary system in the mother		
AVO-incompatibility	↑	
Rh-incompatibility	↑	
Childbirth in the summer season	↑	↑
Birth in the autumn season		↑
Mechanism of childbirth	↑	↑
Apgar at 1st min., 5th min.	↑	
Weeks newborn	↑	
Weight newborn	↑	↑
Breastfed	↑	↑

<u>Task 3</u>. To monitor the dynamics of total bilirubin in full-term newborns until reference limits are reached

Follow-up of the dynamics of BR in the covered group of newborns was accomplished by a total of 2636 measurements using transcutaneous bilirubinometry, of which 1685 were within the hospital stay and the remaining 951 in outpatient examinations. On average, 4.7 measurements were performed per child. The BR values are presented in Fig. 3.1, as from the 1st to the 5th postnatal day they are respectively: 98.4±31.4 μmol/L, 135.5±40.5 μmol/L, 154.4±38.8 μmol/L, 157.2±32.6 μmol/L, 147.3±31.1 μmol/L for the whole group. Around the 14t day, the average level of BR was 125.3±49.5 μmol/L, and 63.8% of NBs were measured of which 68 (19% of the measured and 12% of the whole group) had hyperbilirubinemia and mean levels of BR - 194.0±28.0 μmol/L.

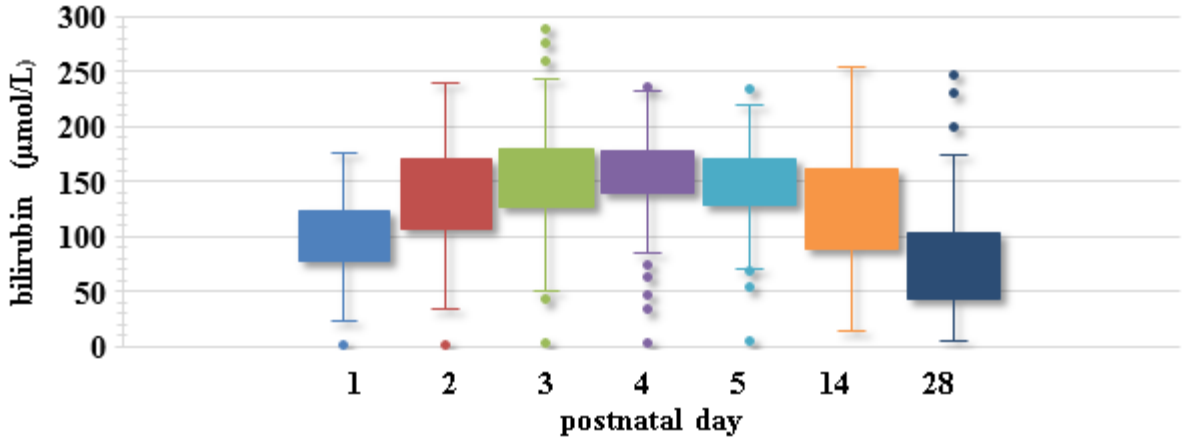

Fig.3.1. Transcutaneous bilirubin levels in 566 full-term newborns from the first to the 30th postnatal day (μmol/L).

Around the 28th day, the average level of BR is 77.6±45.6 μmol/L. On 51.1% of the observed group was performed bilirubinometry, of which 82 children (28% of the measured and 14.5% of the whole group) have HB and a mean value of BR 137.3±30.9 μmol/L. Neonates in whom a transcutaneous BR level was not obtained on days 14 and 28, were visually assessed as not having NJ.

We compared the levels of BR, distributed according to the sex of the observed children, for the entire neonatal period and no significant differences were found (*Fig. 3.2*).

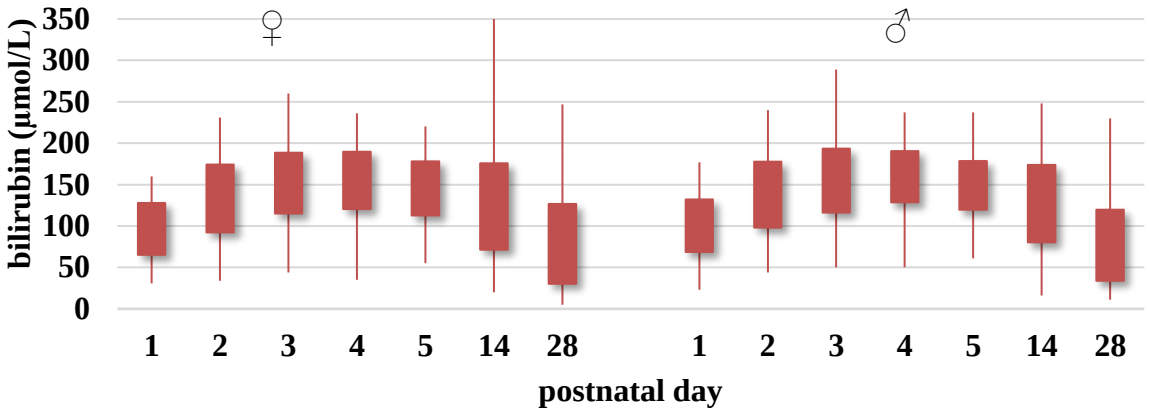

Fig. 3.2. Levels of total bilirubin according to sex by transcutaneous bilirubinometry from day one to day 28 (µmol/L)

We built a nomogram with the measured BR values shown in Fig. 3.3., with five percentile lines (10, 25, 50, 75, 90 percentiles).

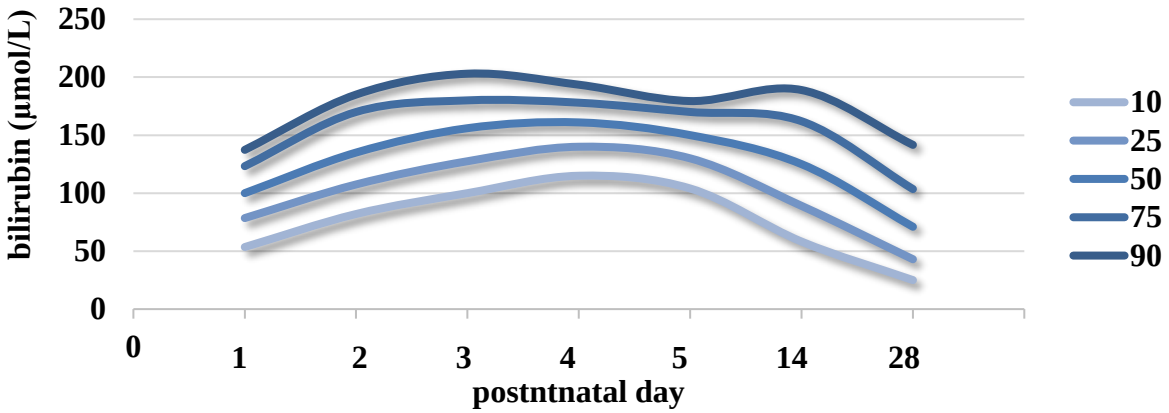

Fig. 3.3. Nomogram of curves from 10th to 90th percentiles for transcutaneous bilirubin levels from day 1 to day 28 in 566 full-term newborn Caucasian children

The current values of the BR by percentiles and the number of measurements per days are presented in Table 3.1. The levels of Bilirubin on the 90th percentile on days from first to fifth, and 14 and 28 are: 137.3 µmol/L, 185.0 µmol/L, 203.0 µmol/L, 193.5 µmol/L, 179.4 µmol/L, 188.9 µmol/L, 141.6 µmol/L.

We calculated the rate with which the level of BR increases from first to second (V_{1-2}), from second to third (V_{2-3}) and third to fourth (V_{3-4}) postnatal day per percentiles 10, 25, 50, 75 and 90 (Fig. 3.4). The values of these velocities up to the 90th percentile do not exceed the limit of 4.3 µmol/L/h, which is recommended by the American Academy of Pediatrics as a borderline risk. Our data on the rate of increase of BR for second, third and fourth day per percentile, compared to those published by De Luca et al. (2008), shows no significant difference.

Table. 3.1. Transcutaneous bilirubin values (in µmol/L) on percentiles 10, 25, 50, 75 and 90 from the first to the fifth, on the 14th and 28th postnatal days.

Day	N	Percentiles				
		10	25	50	75	90
1	188	53.5	78.5	100.0	123.3	137.3
2	364	82.0	107.5	135.0	170.0	185.0
3	473	100.0	127.5	156.0	180.0	203.0
4	364	115.0	140.0	161.0	178.0	193.5
5	215	104.0	130.0	150.0	170.0	179.4
14	350	5.2	89.0	125.0	162.0	188.9
28	285	25.0	43.0	71.0	103.0	141.6

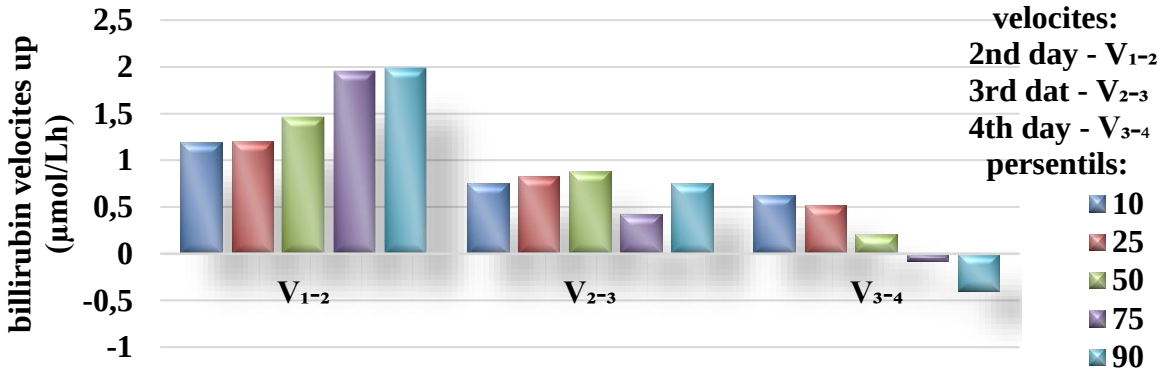

Fig. 3.4. Rate of increase of bilirubin (µmol/L/h) for the 10th, 25th, 50th, 75th and 90th percentiles of second (V_{1-2}), third (V_{2-3}) and fourth (V_{3-4}) postnatal days

However, when comparing the average levels of the total BR, grouped according to the V_{1-2} and V_{2-3} velocities and divided into two groups – above 4.3 µmol/L/h and below this value for the respective days, a significant difference ($p<0.001$) is demonstrated. Newborns who on day three had a recorded rate of increase in BR $V_{2-3}\geq 4.3$ µmol/L/h had significantly higher levels of BR on day 14 (149.3±38.0 µmol/L; p=0.005) and day 28 (98.5±31.7 µmol/L; p=0.008) versus those with less than this value rate of increase in BR (14th day – 123.0±49.8 µmol/L and 28th day – 75.2±46.4 µmol/L) (*Table 3.2*).

Table 3.2. Comparing the mean bilirubin levels (in μmol/L) versus the rate of increase in bilirubin (in μmol/L/h) in the observed group of 566 newborns

Day	***Mean bilirubin values (μmol/L) on the 2nd and 3rd postnatal days and rate of increase of bilirubin – V_{1-2} and V_{2-3} (μmol/L/h)***				
	V<4.3 μmol/L/h		**V≥4.3 μmol/L/h**		**p**
	Bilirubin	**V**	**Bilirubin**	**V**	
2	**129.7±40.4**	**V_{1-2}=1.1±1.9**	**187. 9±22.8**	**V_{1-2}=5.3±0.7**	**<0.001**
3	**138.0±35.0**	**V_{2-3}=0. 2±2.0**	**182.5±28.0**	**V_{2-3}=5.1±0.7**	**<0.001**
	Compared mean bilirubin values (μmol/L) on days 14 and 28 relative to the rate of increase bilirubin V_{1-2} (μmol/L/h)				
	V_{1-2}<4. 3μmol/L/h		**V_{1-2}≥4. 3 μmol/L/h**		**p**
14	**117. 5±55.4**		**127.7±52.0**		**NS**
28	**57.0±37.5**		**83.9±46.0**		**0.06**
	Compared mean bilirubin values (μmol/L) on days 14 and 28 relative to the rate of increase bilirubin V_{2-3}(μmol/L/h)				
	V_{2-3}<4. 3μmol/L/h		**V_{2-3}≥4. 3 μmol/L/h**		**p**
14	**123.0±49.8**		**149.3±38.0**		**0.005**
28	**75.2±46.4**		**98.5±31.7**		**0.008**

Using Pearson's correlation coefficient an assessment was made of the linear relationship between the level of bilirubinemia on day 14 and day 28 and the rate of increase of BR during the early neonatal period. We found a positive correlation between V_{2-3} and the BR level on the 14th ($r=0.368$, $p<0.001$) and 28th ($r=0.580$, $p<0.001$) postnatal day, which can be interpreted as large as or larger than typical.

The traced transcutaneous BR levels in the group with PrNJ show the following dynamics (*Fig. 3.5*): 1st day – 102±24; 2nd day – 151±37; 3rd day – 170±32; 4th day – 171±21; 5th day – 161±27; 14th day – 194±27; 28th day – 145±26; 40th day – 119±34; 50th day – 103±42; 60th day – 90±34 μmol/L. They are significantly higher for all reported measurements compared to the group with FNW ($r<0.001$), in which the following values were measured by days: 1st day – 60.16±15.41, 2nd day – 119.26±31.71, 3rd day – 150.04±35.32, 4th day – 154.01±30.23, 5th day – 146.15±29.64, 14th day – 109.62±38.62, 28th day – 49.35±20.81 μmol/L.

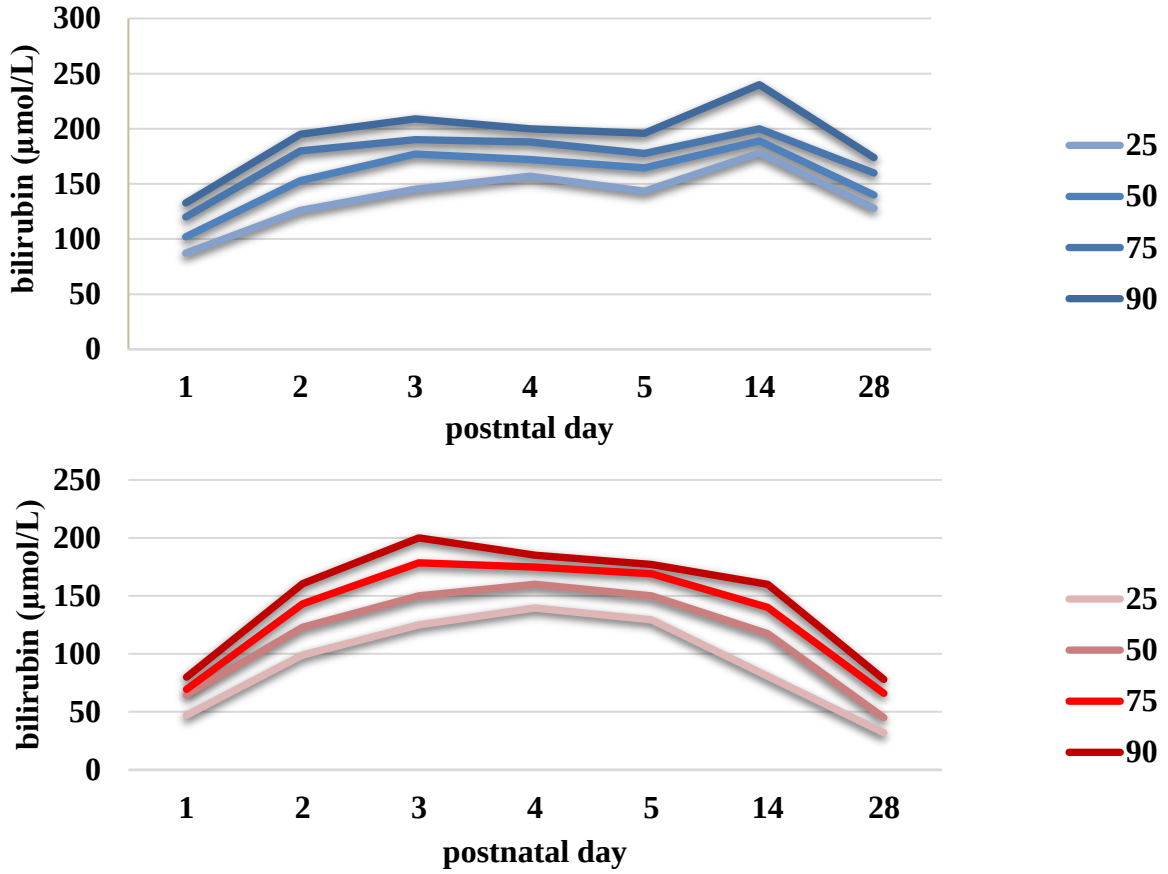

Fig. 3.5. Transcutaneous bilirubin levels (in µmol/L) in groups from first to fifth day, on day 14 and 28 (percentiles and mean levels) in newborns with PrNJ (blue) and PhNJ (in red).

The average duration of clinical manifestation of neonatal icterus (day of recording transcutaneous BR level below 85 µmol/L) is 59±14 days. If the covered newborns are divided into two subgroups – with involution of the NJ up to day 60 and after day 60, and the average level of BR for the observation period is compared, a significant difference in the levels of total BR by the 14th and 28th day ($p<0.001$) is reported. Children with longer manifestation have higher values, respectively (*Fig. 3.6*).

There was a significant difference in the mean levels of total BR depending on the etiology of PrNJ on the 14th ($p=0.001$; $Eta^2=0.273$), on the 28th day ($p<0.001$; $Eta^2=0.827$) and in the duration of PrNJ ($p<0.001$; $Eta^2=0.359$). These differences are presented in Fig. 3.7. Children with abnormalities in the urinary system are those with the longest NJ and the highest average value of BR at the end of the neonatal period. The level of BR at two weeks of age is highest in newborns with inadequate weight gain and/or dehydration.

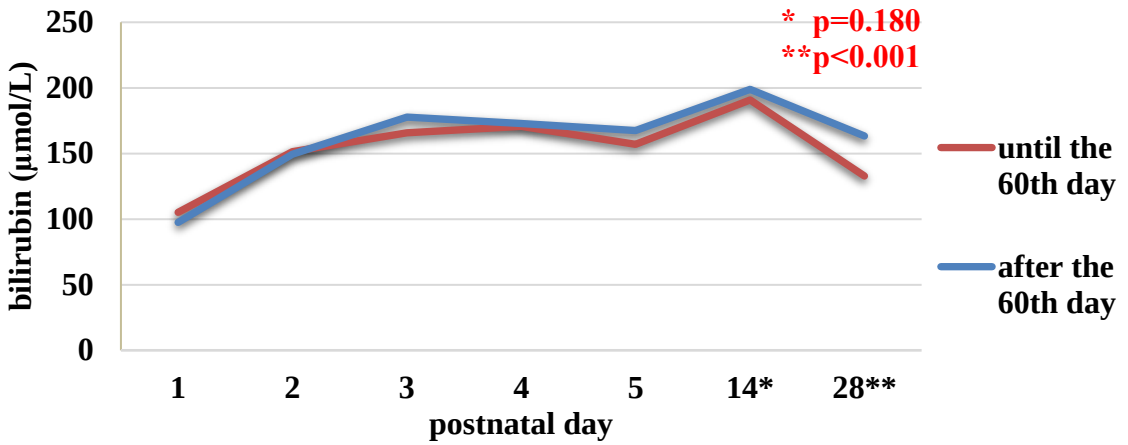

Fig. 3.6. Average levels of total bilirubin (µmol/L) in Group PrNJ according to the duration of NJ – until the 60th and after the 60th postnatal day.

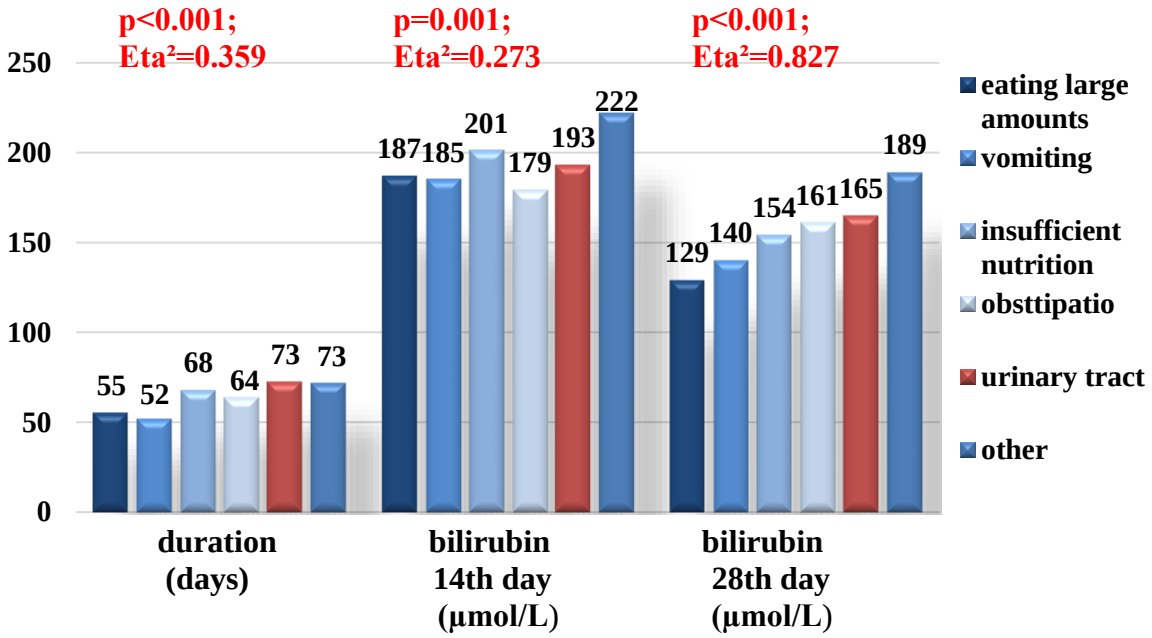

Fig. 3.7. Comparison of bilirubinemia on day 14 and 28 according to the etiological structure of NB with PrNJ.

Conclusion

According to our data, gender is not a determinant of bilirubinemia levels. The rate of increase in total bilirubin in the early neonatal period does not differ from that cited by other authors. The rate of increase of BR above 4.3 µmol/L/h on the third day is a prerequisite for a slower reverse evolution of bilirubinemia and prolongation of LV.

In the case of PrNJ, one must first assess whether the weight gain is adequate and look for an underlying abnormality of the excretory system, as well as rule out a concomitant UTI.

We are the first in Bulgaria to present a nomogram of transcutaneous BR during the neonatal period for full-term newborns. It could be used to identify neonates at increased risk of worsening hyperbilirubinemia after discharge home, in order to develop a follow-up strategy for these children.

<u>Task 4.</u> To study the effect of prophylactic administration of probiotics for prevention of neonatal jaundice

For the purpose of prevention of NJ we applied PB to the NBs. In the current study, we covered 315 NBs who took standard formula (SF) food and supplemented with PB from day one. We divided them into groups from A to G depending on the type of PB which was given and the duration of its application. The data of grouping the patients according to their diet and the type of PB received are presented in Table 4.1. We monitored total Bilirubin levels transcutaneously throughout the neonatal period – from day 1 to day 5 and on day 14 and 28.

Table 4.4. Distribution of the observed newborns in groups according to the diet, intake and type of probiotic.

Groups	***Diet & Type of PB***	***N***	***Days***	***Dose***	***Weight [g]***	***Gestational age [w]***
A	**SF & L. rhamnosus**	**24**	**5**	**6 x 10*9 CFU / 6 d**	**3266.7±408.0**	**38.8±1.3**
B	**SF & L. reuteri**	**16**	**5**	**100 x 10*6 CFU / 5 d**	**3348.1±366.1**	**38.9±1.2**
C	**SF & B. animalis**	**18**	**5**	**1 x 10*9 CFU / 6 d**	**3506.1±503.5**	**38.8±0.9**
D	**SF & L. rhamnosus**	**16**	**30**	**6 x 10*9 CFU / 6 d**	**3476.9±320.5**	**38.8±1.2**
E	**SF,enriched with L. reuteri**	**31**	**30**	**115 x 10*6 CFU / 100 ml**	**3450.0±492.1**	**39.0±0.9**
F	**СФ & B. animalis**	**17**	**30**	**1 x 10*9 CFU / 6 d**	**3173.0±373.8**	**38.3±1.0**
G	**SF without ddition of PB**	**193**	**30**		**3285.3±387.3**	**38.7±1.1**
Total number		**315**			**3316.3±385.5**	**38.8±1.1**

PB – probiotic; w — gestational week; SF – standard formula for newborns (no added PB); d – drops; CFU – colony forming unit

We compared the mean levels of BR between the groups with five-day PB supplementation and the control group. The difference in bilirubinemia was significant between Groups A, B, C, G on second, third and fourth day (2nd day $p<0.001$; 3rd day $p=0.010$; 4th day $p=0.040$). The lowest transcutaneous levels of total BR were recorded in group C (*Figure 4.1*) from day 2 to day 5 respectively: 87.3±28.8 μmol/L; 115.9±40.9 μmol/L; 128.4±33.6 μmol/L; 130.9±29.2 μmol/L. The highest levels of BR for the same period were those in Group G from

the second to the fifth day, respectively: 143.8±35.8 μmol/L; 162.8±34.0 μmol/L; 160.6±29.0 μmol/L; 143.3±30.0 μmol/L.

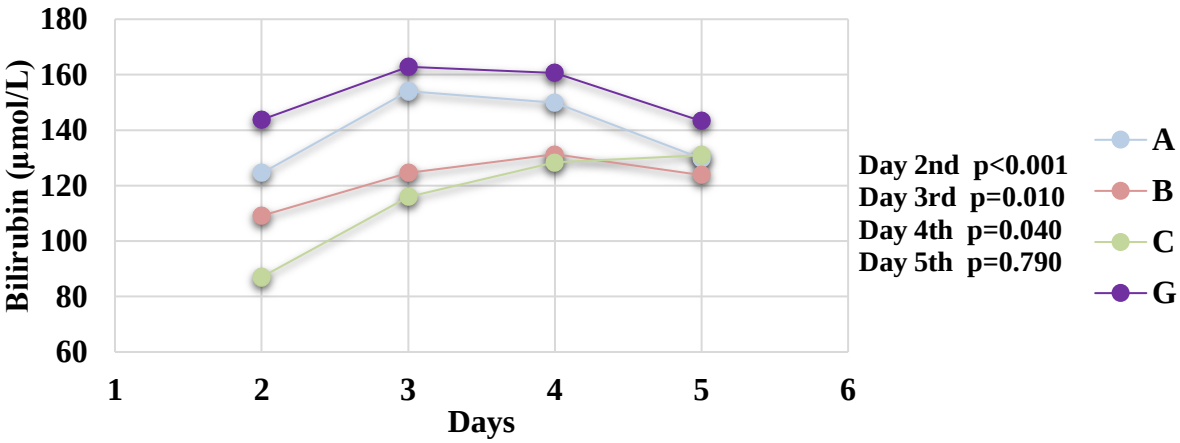

Fig. 4.1. Comparison of mean levels of total bilirubin (μmol/L) from day two to day 5 between the 5-day probiotic groups (A, B, C) and the control group G.

We compared the mean levels of total BR measured in Groups D, E and F who had been taking PB throughout the neonatal period with the control Group G. We found a statistically significant difference for the period from the second to the fourth day and on the 14th and the 28th day (2nd day p=0.001; 3rd day p<0.001; 4th day p=0.001; 5th day p=0.061; 14th day p=0.014; 28th day p=0.029). The highest levels of BR for the follow-up period were recorded in group G (*Fifure 4.2*) and the lowest in Group F (*Figure 4.2*).

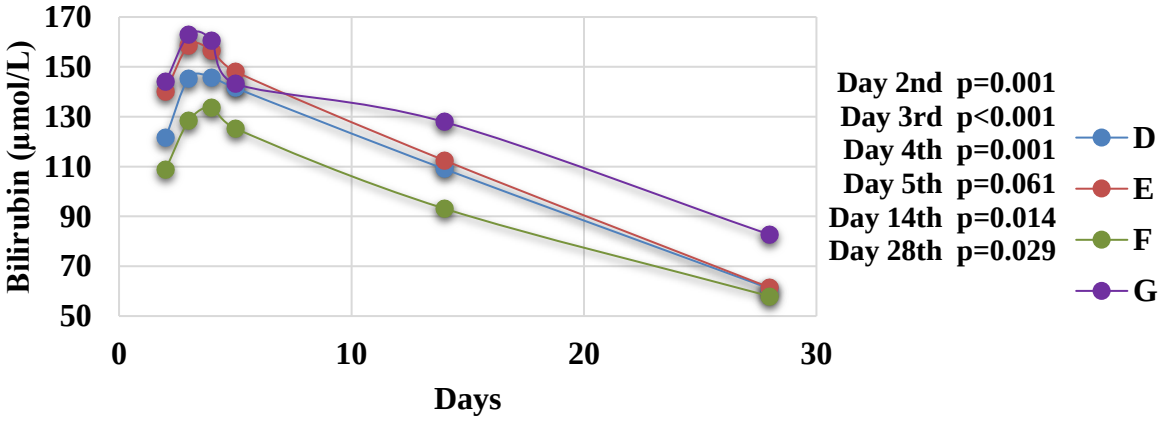

Fig. 4.2. Comparison of mean levels of total bilirubin (μmol/L) between groups with 30-day probiotic intake (D, E, F) and control Group G

When comparing the mean values of the BR on day 14 and 28 of groups with complementation of PB for the entire neonatal period (D, E, F) and those with PB intake only during the first 5 days (A, B, C) we found a statistically significant difference. The highest levels of BR were reported in the control group G on day 14 (127.9±46.9 μmol/L) and day 28t

(82.6±42.5 µmol/L), and the lowest levels – in Group F on day 14 (93.1±43.1 µmol/L) and day 28 (57.9±36.1 µmol/L) (p=0.009; p=0.010). Among the groups with PB intake throughout the neonatal period, the highest BR levels had Group D – on day 14 (112.5±47.3 µmol/L) and on day 28 (61.4±48.5 µmol/L) (*Fig. 4.3*).

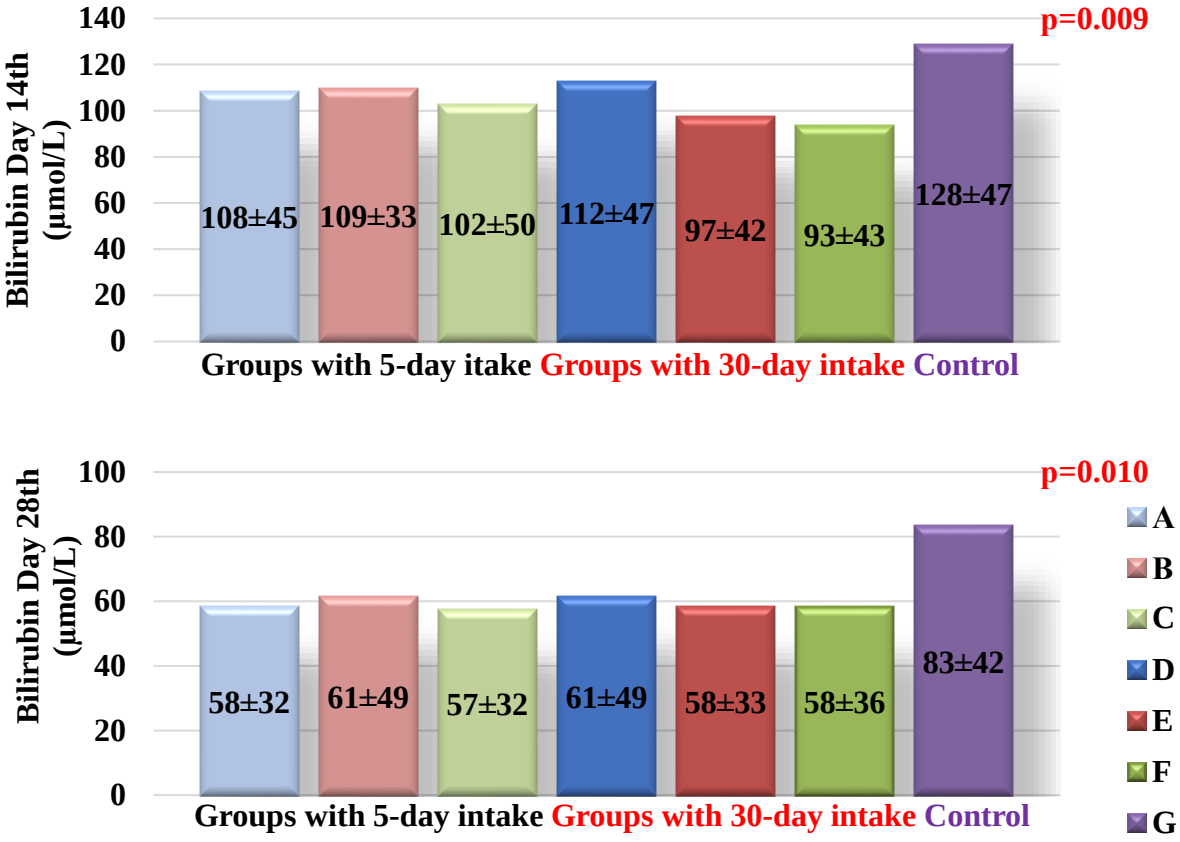

Fig. 4.3. Mean bilirubin levels (µmol/L) on day 14 and 28 by groups A to G.

We compared the percent of NBs with registered PaNJ in the groups according to the type of PB supplemented for the first 5 postnatal days and found a difference. In A&D groups with L. rhamnosus intake, 37% of the NBs had PaNJ, in B&E groups supplemented with L. reuteri – 36%, and in Groups C&F with added B. animalis – 29%. In the control Group G, PaNJ was found in 44% of the children (*Fig.4.4*). Accordingly, the proportion of patients requiring PhT was significantly different according to the type of PB supplemented: in Groups A & D – 37.5%, Groups B & E – 42.6%, Groups C & F – 25.7% and Group G – 50.8% (p<0.001) (*Fig. 4.5*).

We report a significant difference in hospital stay according to the admitted PB. The control group has the longest – 4.7 days, and for the groups with intake of B.animalis and L. reuteri have the shortest – 4.1 days (p<0.001) (*Fig. 4.6*).

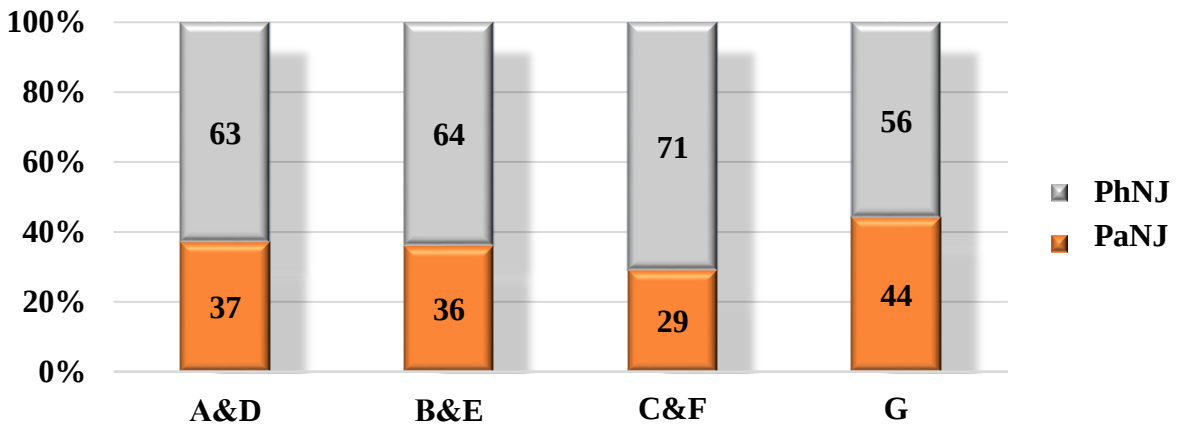

Fig.4.4. Proportion of newborns (in %) with pathological neonatal jaundice in groups according to the type of supplemented probiotic for the first 5 postnatal days (PaNJ – pathological neonatal jaundice, PhNJ – physiological neonatal jaundice or without jaundice).

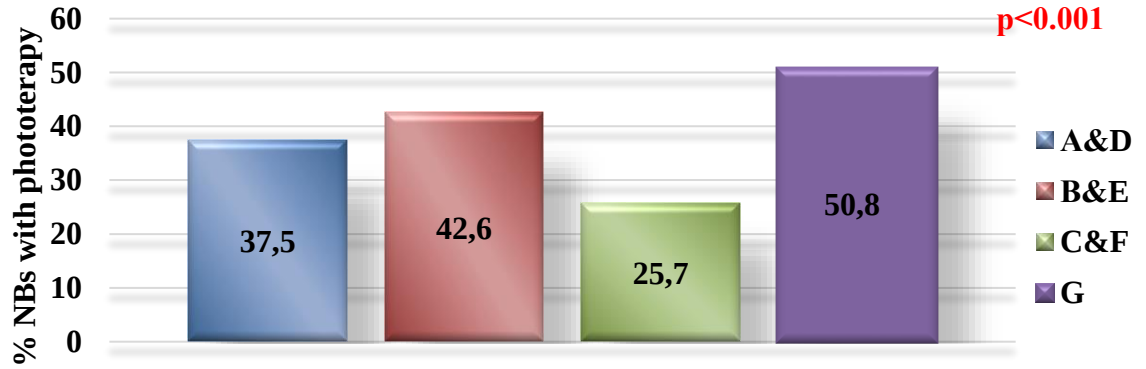

Fig. 4.5. Share of newborns with phototherapy (in %) by groups according to the type of intake of probiotic

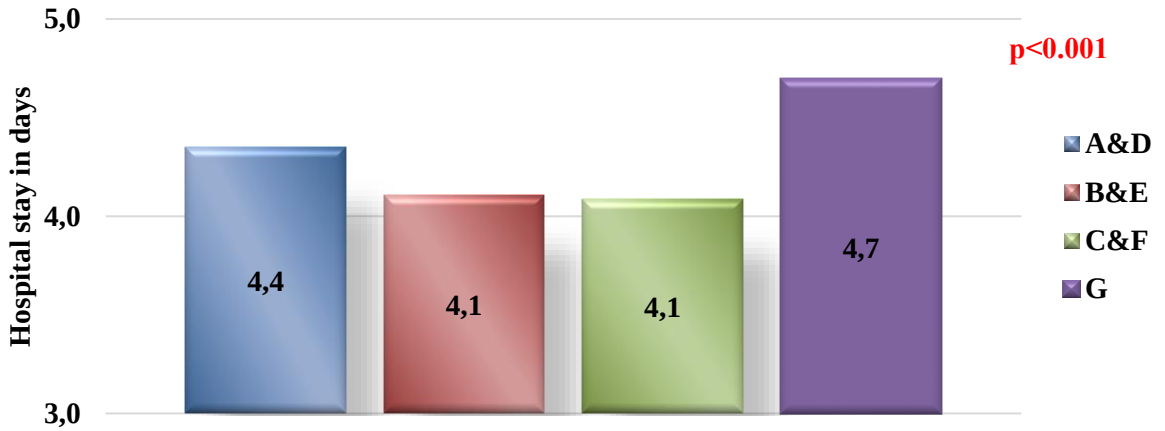

Fig.4.6. Average hospital stay (days) by groups according to the type of intake of probiotic

Conclusion

According to our data, the prophylactic use of Lactobacillus rhamnosus, Lactobacillus reuteri and Bifidobacterium animalis in full-term neonates significantly reduced the frequency and duration of NJ, as well as the duration of phototherapy. This effect is most pronounced with Bifidobacterium animalis and least pronounced with Lactobacillus reuteri.

The duration of the probiotic course significantly influenced the evolution of NJ in full-term NB. The best effect is achieved when taking PB throughout the neonatal period or until complete involution of jaundice.

<u>Task 5.</u> To monitor the neuropsychiatric development, weight curve and hemoglobin levels of newborns with prolonged neonatal jaundice until the age of six months.

In the research are included 92 full-term NBs with PrNJ, born from January, 2017 to October, 2020, passed through the Neonatal Department of University Hospital Medica Ruse Ltd, who had indirect HB and only PhT was performed as a method of NJ treatment. The gender distribution shows that 55(60%) are boys, 37(40%) are girls. The average gestational age is 38.5±1.0 years, with ≤38 years. are 49(53%)and ≥39 years old. are 43(47%). The average weight is 3374.4±401.1 g, with the majority of the children weighing 3000-3999 g (70%).The delivery by cesarean section is in 50(54%) of the group (22% of those born by cesarean section are delivered by emergency). For comparison, we used a control group PhNJ including 227 children who did not show jaundice or had physiological jaundice. There was no statistically significant difference between the groups in gestation age, birth weight, sex distribution, mechanism of birth and Apgar score (*Table 2.2*).

On the first postnatal day, 35(38%) of NBs with PrNJ had clinically manifest icterus, in the first week – 40(44%). By day 14, BR values above 171 μmol/L were recorded in 80 NB(87%) of the observed group. On day 28, all 92 children had a BR level above 90 μmol/L. At the end of the second month, 35(38%) of the children still had HB, by the end of the third month the icter underwent reverse evolution in all observed (*Fig.5.1*). Persistent NJ by day 60 had 37% of NBs with HB on day one and 30% of children with HB in the first week.

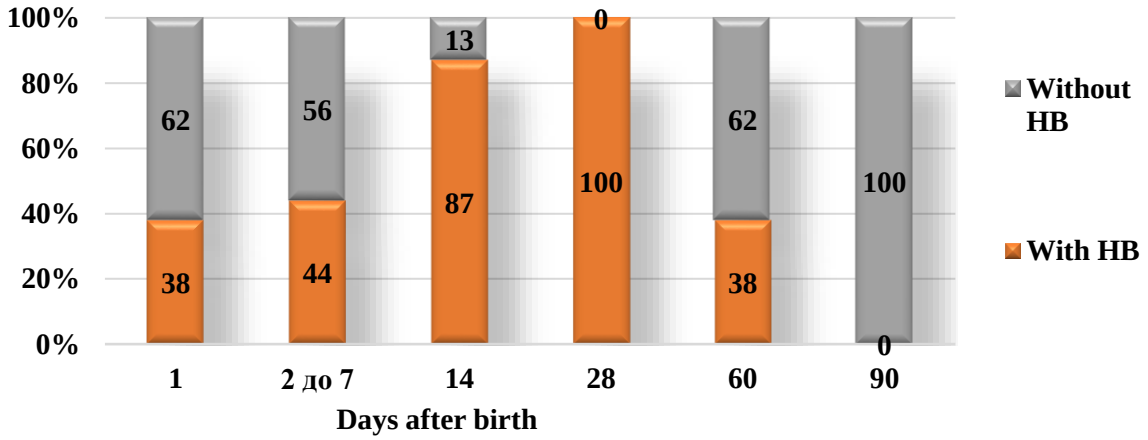

Fig. 5.1. Proportion of NBs with hyperbilirubinemia (in %) from the first day to the end of the third postnatal month in Group PrNJ.

We followed the weight gain of the children of Group PrNJ from birth to 6 months of age and visualized the data with a diagram (*Fig.5.2*). The average weight of Group PrNJ at 6 months of age was 7599.5±980.5 grams. The observed Group PrNJ gained an average of 709±140.8 g/month. The average weight at 6 months of age and the weight gain of up to 6

months do not differ statistically from the data in the body mass tables according to Appendix №1 of Ordinance №2 of 4 February 2003 on the Organization and conduct of prophylactic examinations in persons from 0 to 18 years and dispensary monitoring of compulsory health-insured persons.

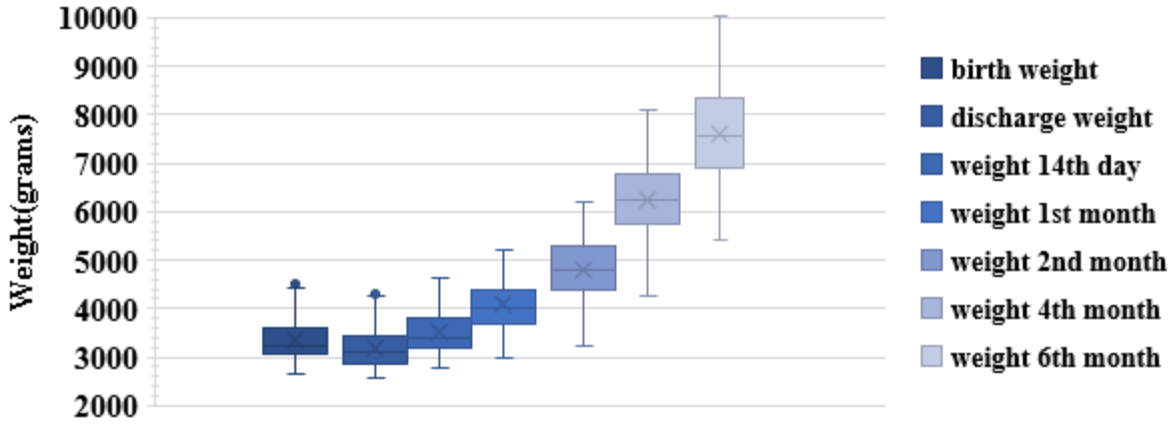

Fig.5.2. Weight changes in Group PrNJ from day one to 6 months of age

Pearson's correlation coefficient (r) between the BR level on day 28 and the weight drop in % at the fifth postnatal day (r=-0.218, p=0.037) showed a moderate negative relationship. The coefficient of determination is 5%. The linear regression between these indicators is shown in Figure 5.3.

Pearson's correlation coefficient (r) between the BR level and the weight gain in % on day 28 (r=-0.188, p=0.043) showed a weak negative relationship. The coefficient of determination is 3.5%. The linear regression between these indicators is shown in Figure 5.4.

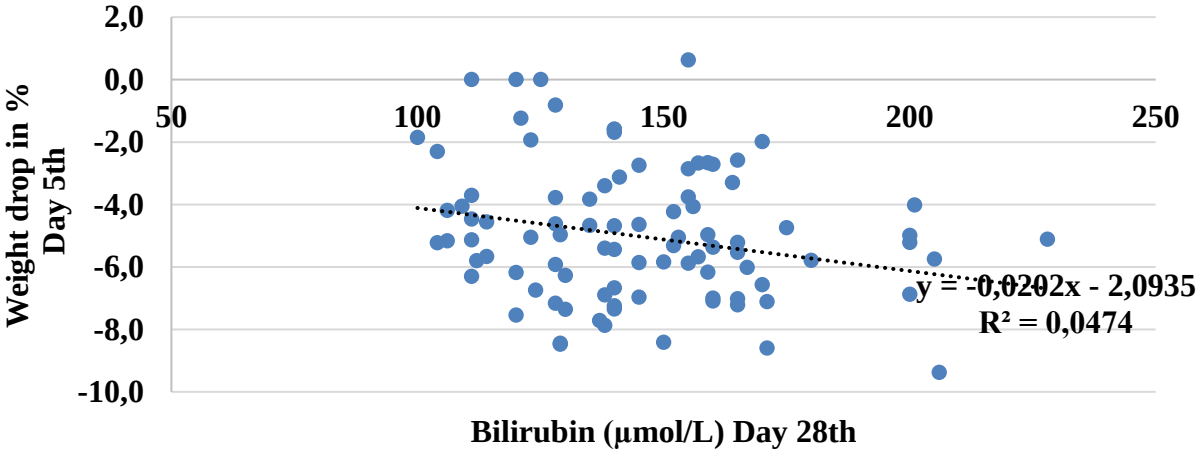

Fig.5.3. Relation between the weight lost (in %) on the fifth postnatal day and the value of bilirubin on day 28 in NB with PrNJ.

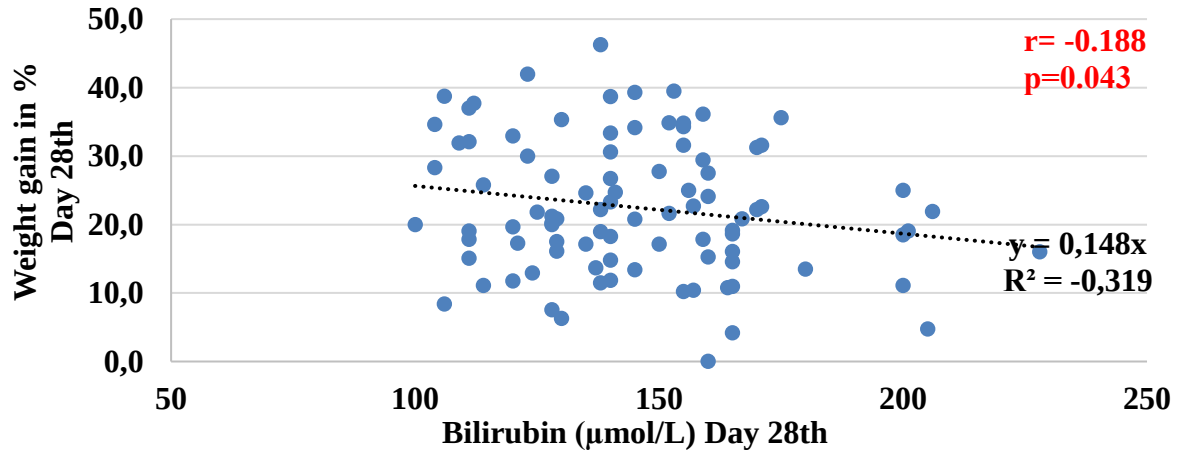

Fig.5.4. Relationship between weight gain (in %) and bilirubin value at day 28 in NB with PrNJ

The average level of Hgb in Group PrNJ on the first day is 183.3±21.6 g / L. 13% of them are with anemia and with polycythemia - 34%. The mean value of Hgb at 6 months of age is 107.8±12.1 g/L. 58% of the observed group have anemia. Half of the anemic children at 6 months of age are with iron deficiency (*Table 5.1.*).

We investigated the correlation between hemoglobin level on the first postnatal day and BR level at the end of the neonatal period using a Pearson's coeffient. A moderately strong relationship was found between these indicators (r=0.220, p=0.035) with a coefficient of determination of 5%. The linear regression between these indicators is shown in Figure 5.5. A strong relation (r=0.509, p<0.001) with a coefficient of determination of 26% was found between Hgb levels on day one and Hgb levels at 6 months of age with the same correlation analysis. In Figure 5.6 their linear regression is presented.

Table 5.1. Laboratory parameters in Group PrNJ

Parameter	***N (%)***	***Value***	***Correlation***	
			p*	***r***
Hвb 1st day (g/L)	**92**	**183.3±21.6**	**p=0.035**	**BR day 28th**
Hвb 6th months(g/L)	**92**	**107.8±12.1**	**p<0.001**	**Hвb 1st day**
Iron	**34 (37%)**	**7.8±2.0**		
BR day 14th (µmol/L)	**92**	**194.0±27.4**	**p=0.001**	**BR day 28th**
BR day 28th (µmol/L)	**92**	**145.1±26.3**	**p<0.001**	**Durations of PrNJ**

**p<0.05*

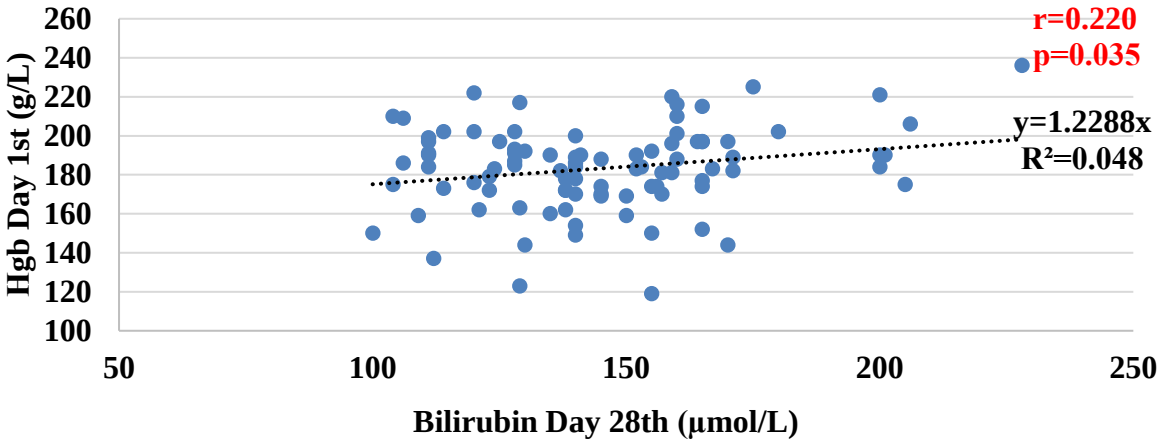

Figure 5.5. Relationship between the value of Hgb (g/L) on day one and bilirubin levels (µmol/L) on day 28 in Group PrNJ

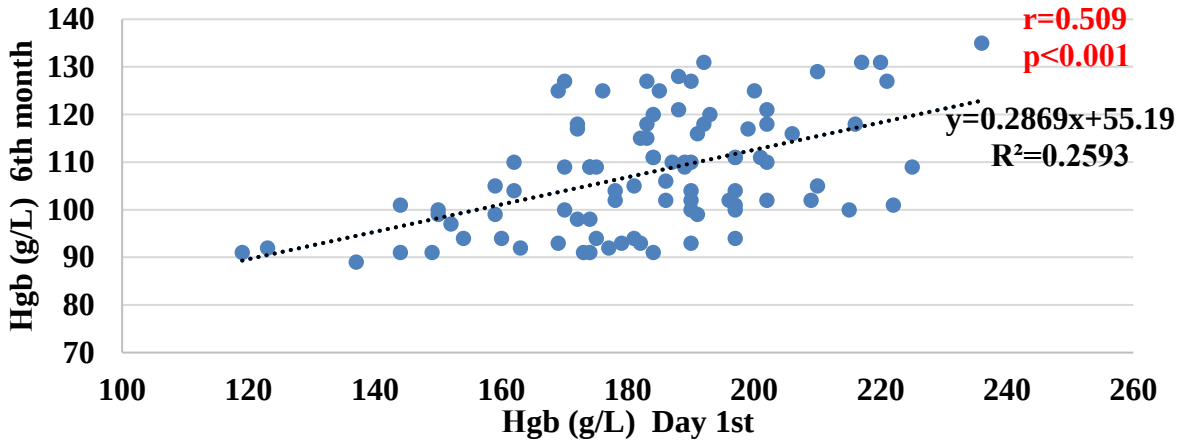

Figure 5.6. Relationship between Hgb levels (g/L) on day one and Hgb levels (g/L) on 6th months at Group PrNJ

We compared the Hgb levels of children at 6th months of age in Group PrNJ, dividing them according to the presence or not of maternal anemia during pregnancy. In anemic mothers, the measured Hgb of their children was 94.9±5.3 g/L, and in children whose mothers did not have anemia, Hgb was 112.8±10.2 g/L, the difference being significant ($p<0.001$). We investigated the correlation between hemoglobin level at 6 months and Maternal Anemia during pregnancy using a Pearson's coefficient. A moderately strong association was found between these indicators ($r=0.670$, $p<0.001$).

We assessed the influence of hyperbilirubinemia on neurological status in Group PrNJ by using the bilirubin toxicity coefficient – BIND-M during examination on day 14. The average BIND-M value was 1.5±1.2. Children with a coefficient from 1 to 3 (66.3%) predominate, 29.3% have a value of 0, two have a coefficient of 4 (2.2%), two - with a coefficient of 5 (2.2%) (*Fig.*5.7).

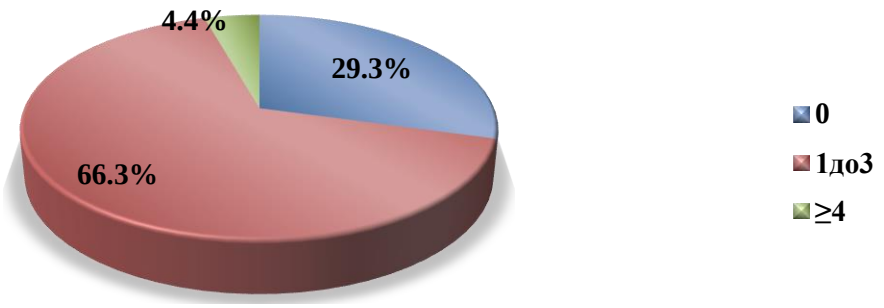

Figure 5.7. BIND-M (modified bilirubin induced neurologic dysfunction score) calculated at 14.5±4.9) postnatal day in Group PrNJ

We followed and compared children in Group PrNJ and Group PhNJ by calculating CoD (coefficient of development) neuro-mental development of from birth to the 24th postnatal week every 4 weeks. The NBs with PrNJ showed significantly lower CoR values for the whole observation period (*Fig. 5.8*).

Using Pearson's correlation analysis, we looked for an association between the two indicators – CoD at week 4 and BIND-M, and found a strong negative correlation between them (r=-0.731, p<0.001). The coefficient of determination is 53%. The linear regression between the two indicators is shown in Figure 5.9. In one of the children with a coefficient 5 BIND-M PrNJ is associated with malnutrition. After correcting the diet and registrating a positive weight curve, HB underwent reverse development until day 60 and CoD at the age of 24 weeks was 100. The other child with a coefficient 5 BIND-M PrNJ was based on hemolysis (ABO incompatibility). HB lasted until day 90 with no neurotoxic levels of total BR recorded. However, CoD at 24 weeks. is 86, which is a lower limit value for that age.

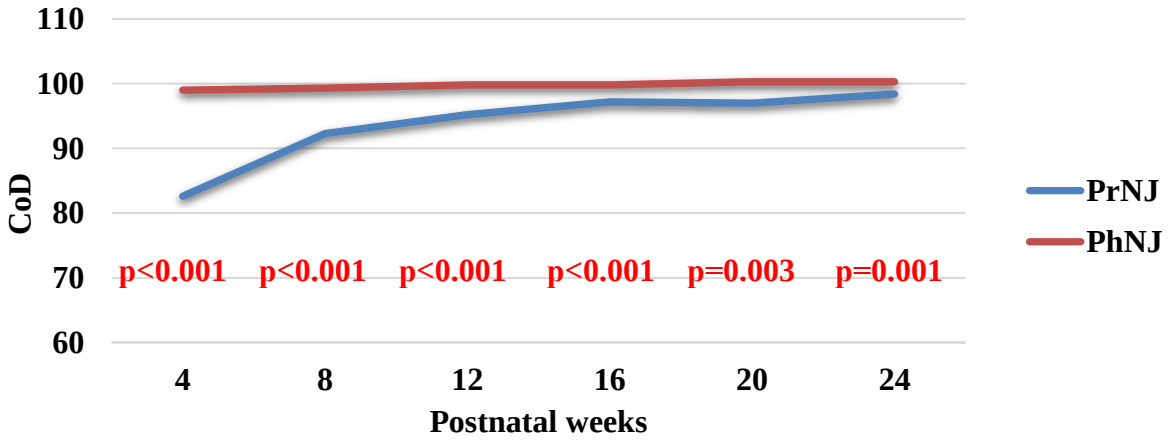

Fig.5.8. Comparison CoD of Group PrNJ and Group PhNJ

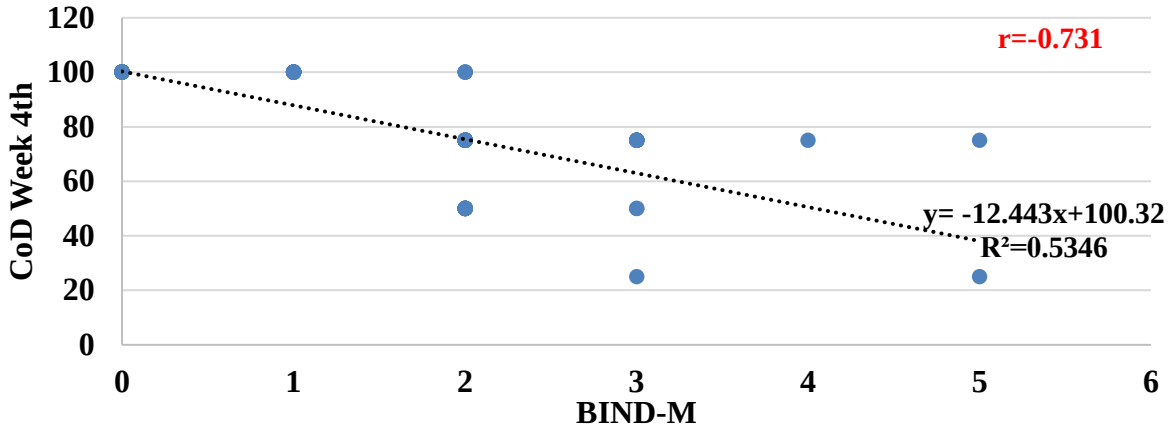

Fig.5.9. Relation between CoD at 4 weeks of age and BIND-M in Group PrNJ

Conclusion

The use of BIND-M and CoD is an easy and convenient way to objectify the current condition of a child with NJ and predict the neurological prognosis.

Inadequate weight gain in the first postnatal month is an aggravating factor for prolongation of NJ. The level of BR at the end of the neonatal period is a predictor of the duration of presentation of PrNJ.

Anemia of the mother (based on low levels of serum iron) and of the newborn in combination with prolonged jaundice of the hemolytic type are prerequisites for the persistence of anemic conditions in infancy with iron deficiency also being recorded

V. CONCLUSIONS

1.According to our data, the incidence of pathological forms of indirect hyperbilirubinemia in the first 2 weeks of life in full-term newborns is 38.9%, and in 14.5% of all children it prolongs until the end of the neonatal period.

2.Most often, pathological forms of NJ are due to hemolysis, a consequence of ABO-isoimmunization, and prolongation of NJ is most commonly observed in exclusively breastfed newborns with digestive problems. Despite the established abnormalities in the structure of the excretory system in part of the NBs with PrNJ, we did not find an accompanying urinary tract infection as a reason for prolongation of the NJ.

3.NJ is a specific condition for the neonatal period of multifactorial etiology. We believe that the combination of different factors – vaginal birth, birth sequence, history of NJ in previous sibling, younger gestational age, lower weight, asphyxia, younger age of the mother, pathology of pregnancy (th reatening premature birth, infections of the reproductive or urinary systems), exclusive breastfeeding, is a prerequisite for the manifestation of HB in NB.

If thyroid function is well controlled, as well as a balanced iron supplementation of the pregnant woman, these conditions will not affect the degree of bilirubinemia in the newborn. Preeclampsia and hypertension during pregnancy reduce the risk of developing HB in full-term newborns.

We do not prove an influence of NB gender on the frequency and extent of PaNJ expression.

4. Probiotic bacteria can affect the frequency and clinical course of NJ by inhibiting the multiplication of pathogens in the gastrointestinal tract of NB, reducing the enterohepatic circulation of BR and directly interfering with its intestinal metabolism.

According to our data, the prophylactic use of Lactobacillus rhamnosus, Lactobacillus reuteri and Bifidobacterium animalis in full-term newborns significantly reduces the frequency and duration of NJ as well as the duration of phototherapy. The most pronounced effect is observed with the administration of Bifidobacterium animalis and the least pronounced – with Lactobacillus reuteri.

The duration of the probiotic course is also relevant for the evolution of NJ in full-term NB. The best effect is achieved by taking PB throughout the neonatal period or until complete involution of NJ.

5. Prolongation of the NJ is observed more often in those born in the summer. Predictors of the development of PrNJ are the rate of increase of BR during the early neonatal

period and the inadequate weight gain during the first postnatal month. The retention of higher levels of BR at the end of the neonatal period gives an indication of its duration.

Children with PrNJ have delayed neuro-mental but not physical development during the first 6 months. The prognosis of PrNJ is favorable in 96.7% of cases.

Our observations showed that neonatal jaundice is a multifactorial condition typical for the neonatal period, which most often has a favorable prognosis. Prolongated neonatal jaundice requires systematic monitoring and evaluation of psychomotor development to avoid long-term neurological disability.

Probiotics have a place in the prevention of neonatal jaundice, but larger studies are needed to refine the strain that are most appropriate to use for this purpose, the duration of the course, the dose, possible side effects.

VI. CONTRIBUTIONS

OF A SCIENTIFIC-THEORETICAL NATURE:

1. For the first time in Bulgaria there is a study on the frequency and clinical manifestation of neonatal jaundice in full-term newborn children.

2. For the first time in Bulgaria an in-depth analysis of the etiological structure of PaNJ and PrNJ is made.

3. For the first time in Bulgaria, the influence of perinatal factors on the risk of development and the clinical course of PaNJ and PrNJ is studied.

OF A SCIENTIFIC-APPLIED NATURE:

1. For the first time in Bulgaria, in full-term newborns, the dynamics of serum levels of total bilirubin are monitored until reference values are reached, and based on this, a nomogram of transcutaneous bilirubin levels for the neonatal period is constructed, which can be used in clinical practice to control neonatal bilirubinemia and avoid the toxic effects of bilirubin.

2. For the first time in Bulgaria, NBs with PrNJ are tracked, their development is assessed and markers are indicated for predicting the risk of prolongation of NJ and the duration of PrNJ, namely the rate of growth of BR during the early neonatal period and the value of serum BR at the end of the neonatal period. This would allow newborns at risk to be identified and followed up adequately after discharge home.

For the first time in Bulgaria, the influence of probiotics on the frequency and rate of manifestation of NJ in full-term newborns is studied, and for the first time in the world the effects of prophylactic administration of probiotics on bilirubinemia in NJ are compared.

VII. SCIENTIFIC PUBLICATIONS AND PARTICIPATIONS RELATED TO THE DISSERTATION

Scientific publications related to the dissertation

1. Itova T., Georgieva V.. PROBIOTIC PROPHYLAXIS OF NEONATAL JAUNDICE. *Journal of Biomedical and Clinical Research*. 2022;15(2): 158-164. https://doi.org/10.2478/jbcr-2022-0022

2. Itova T, Atanasova V. FOLLOW-UP OF NEWBORNS WITH INDIRECT PROLONGED HYREBILIRUBINEMIA. *MedMag*;116(9):60-67

3. Itova T, Atanasova V. DYNAMICS OF TOTAL BILIRUBIN DURING THE NEONATAL PERIOD IN TERM NEWBORN. kij [Internet]. 2021 Dec. 15 [cited 2023 Apr. 6];49(4):739-44. Available from: https://ikm.mk/ojs/index.php/kij/article/view/4551

4. Itova, T; Atanasova, V. NONINVASIVE MEDIATION OF BILIRUBIN IN TERM NEONATES. Selected Abstracts of the 16th International Workshop on Neonatology, Virtual Edition (Cagliari, Italy; 29-30 October, 2020) & of the 16th International Congress on Neonatology and Pediatrics, On Demand (Cagliari, Italy; November 20-December 31, 2020). *J Pediatr Neonat Individual Med* [Internet]. 2020Dec.17 [cited 2023Apr.3];10(1):e100107. Available from: https://jpnim.com/index.php/jpnim/article/view/e100107

5. Itova TD, Georgieva VA. PRENATAL FACTORS FOR NEONATAL JAUNDICE. *J of IMAB*. 2022 Oct-Dec;28(4):4660-4665.DOI: 10.5272/jimab.2022284.4660

Participation in scientific forums in Bulgaria

1. NEONATAL JAUNDICE IN FULL-TERM NEWBORNS – FREQUENCY AND ETIOLOGY /poster/
   VIth National Conference on Neonatology
   12–14.10.2018 Bulgaria, Tryavna.

2. PROBIOTICS AND NEONATAL JAUNDICE /presentation/
   VIIth National Conference of Neonatology
   11-13.10.2019 Bulgaria, Burgas.

3. PROBIOTIC PROPHYLAXIS OF NEONATAL JAUNDICE /presentation/.
   4th Congress of Neonatology
   08-10.10.2021 Bulgaria, Starosel

4. FOLLOW-UP OF NEWBORNS WITH PROLONGED NEONATAL HYPERBILIRUBINEMIA /oral poster/.
   15th National Congress of Pediatrics.
   23-26.09.2021 Bulgaria, Borovets

Participation in international scientific forums :

5. PROBIOTICS FOR PREVENTION OF NEONATAL JAUNDICE /poster/.
   10th International Congress of UENPS,
   18-21.11.2020 Italy, Rome

6. NONINVASIVE NEASUREMENT OF BILIRUBIN IN TERM NEONATES
   16th International Workshop on Neonatology • Virtual Edition & of the 16th International Congresson Neonatology and Pediatric
   29-30.10. 2020 , 20.11-31.12.2020 Italy, Cagliari

7. PERINATAL FACTORS AND MANIFESTATION OF NEONATAL JAUNDICE /poster/
   European congress of perinatal medicine
   14-17.07.2021 Portugal, Lisbon
8. JAUNDICE FROM BREAST MILK / oral poster/
   3rd Euro-global conference on pediatrics and neonatology
   17.09.2021 France, Paris

9. WHICH PROBIOTIC IS MOST SUITABLE FOR THE PREVENTION OF NEONATAL JAUNDICE? /oral presentation/
   7th International congress on probiotics, prebiotics, postbiotics in pediatrics
   7-9.10.2021 Spain, Valencia

DECLARATION OF ORIGINALITY

By Tatyana Dimitrova Itova – PhD student at the Medical University Pleven.

I declare that the dissertation presented for consideration on the topic: "Jaundice in full-term newborn children – frequency, etiology, prevention, follow-up" with scientific leaders Assoc. Dr. Nikolay Balgaranov, MD, PhD and Assoc. Dr. Victoria Atanasova, MD, PhD was prepared and written by me personally, as the sources used are correctly presented and cited.

Pleven 2023 .....

(T.Itova)