

Unconjugated Pathological Jaundice in Newborns

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ABSTRACT

Neonatal jaundice is the occurrence of elevated bilirubin levels in the blood. It may be physiological or pathological. If the concentration of non-conjugated bilirubin in the blood is too high, it breaches the blood brain barrier and bilirubin encephalopathy occurs with serious consequences for the child. The aim of the research was to examine the incidence frequency of unconjugated pathologic jaundice in newborns and connect it to some epidemiological variations (medical, social, demographic) as well as to prove the increased frequency of jaundice in children born by stimulation and labour induction. The study included 800 infants: 198 (24.8%) of them did, and 602 (75.2%) did not suffer from jaundice. Statistical analysis confirmed the association between the onset of jaundice in newborns and the following parameters: gestational age, birth weight, maternal infections and other illnesses during pregnancy and premature rupture of membranes as complications during labor and the mode of delivery.

Key words: newborns, unconjugated jaundice, bilirubin encephalopathy, mode of delivery, risk factors, preeclampsia, complications in pregnancy

Introduction

Newborn jaundice is the occurrence of elevated bilirubin levels in the blood. It may be physiological or pathological. Physiological neonatal jaundice (occurring due to immaturity of the newborn's liver and higher concentrations of bilirubin from haemolyzed erythrocytes) is manifested in increased concentration of unconjugated bilirubin during the first days of a newborn's life, reaching a maximum concentration of 205 $\mu\text{mol/L}$. The bilirubin then returns to normal levels by the end of the second week following full term birth, i.e. third week with preterm newborns. Physiological hyperbilirubinemia has an incidence of 20–50% in full-term newborns. The three types of pathological jaundice are *icterus praecox* (if it has been noticed in the first 24 hours following birth), *icterus gravis* (if the level of serum bilirubin exceeds 205 $\mu\text{mol/L}$ in full-term and 255 in preterm newborns) and *icterus prolongatus* (if jaundice persists after the end of the newborn's second or third week). Pathological unconjugated hyperbilirubinemia is a condition in which the serum is elevated only at the unconjugated bilirubin level. The causes of unconjugated jaundice may be divided into two groups. The first group includes the conditions and diseases that are characterized by increased de-

livery of bilirubin to hepatocytes: haemolytic disease of the newborn caused by fetomaternal isoimmunization, hereditary haemolytic anaemia, blood haemolysis in large haematoma or effusion, increased enterohepatic circulation during slow intestinal passage (hypothyroidism, meconium ileus, intestinal obstruction). The conditions forming the second group are those resulting in a decreased conjugation of bilirubin in the liver (e.g. *icterus prolongatus* in newborns that are breastfed (lactation jaundice)), as well as the conditions in which newborns have congenital hypothyroidism and delayed maturation of UDPG-T (a hereditary defect in the enzyme UDPG-T). Certain mechanisms of jaundice genesis in the same child may operate jointly: sepsis causes enhanced haemolysis, but it also damages hepatocytes directly.

Neonatal jaundice is extremely significant: if the concentration of non-conjugated bilirubin in the blood is high, it breaches the blood brain barrier and causes permanent damage with serious consequences for the child. In addition to the bilirubin concentration, the development of bilirubin encephalopathy depends on many other factors. Bilirubin may pass through the blood-brain bar-

rier as a free bilirubin (unbound to albumin) or in case the blood-brain barrier is interrupted. Various anions can displace bilirubin from albumin (hematin, bile salts, free fatty acids, drugs such as digoxin, diazepam, salicylates, sulphonamides, sodium benzoate). Acidosis, hypoxia, hypoalbuminemia, hypothermia and possibly other unknown factors foster the development of *kernicterus*. Clinical manifestation usually occurs between the second and fourth day following birth in the form of lethargy, poor sucking, screeches, vomiting and muscle hypotonicity, that are quickly followed by hypertonus, opisthotonus and cerebral convulsions. Lethality is high due to central respiratory failure and children who survive the acute phase tend to develop cerebral palsy with choreoathetosis, deafness and impaired mental function.

The treatment of infants with unconjugated pathological jaundice is associated with the cause of jaundice. Early detection of possible jaundice causes allows for a timely diagnosis as well as treatment. Bilirubin may be mechanically removed from the bloodstream by transfusion, thereby allowing for its excretion to be increased by phototherapy. Alternatively, bilirubin metabolism can be accelerated by administering medications such as fenobarbital^{1,2}.

Labour induction is an obstetric procedure applied in order to stimulate uterine contractions and labour. Oxytocin and prostaglandins are nowadays most commonly used for the purpose of labour induction. According to indications, induced labour may be divided into induced applied for social and preventive reasons and induced therapeutic. The greatest risk of labour induction is the unexpected prematurity as a result of inadequately estimated fetal gestational age^{3,4}. Several scientists have associated increased bilirubin levels in neonates following labour induction using oxytocin, under the assumption that oxytocin acts as vasopressin causing osmotic edema with subsequent erythrocyte hemolysis^{5,6}.

Material and Methods

The study was conducted at the Department of Pediatrics of the University Hospital of Osijek. The data were sourced from the medical records of the Department. The study included all infants born over a period of four months (from the beginning of August until the end of December of the same year, except for those with severe disabilities which were transported to NICU), with a total of 800 newborns. Of the 800, jaundice was not diagnosed in 602 (75.2%) newborns and was diagnosed in the remaining 198 (24.8%), who underwent phototherapy. The data collected from the newborns were categorized by gender, birth weight and gestational age. The following parameters were recorded in mothers of newborns: age, birth weight, gestation, complications during pregnancy and during labor and the mode of delivery. The data relating to the jaundiced newborns were further analyzed according to some of the possible causes of jaundice (systemic infection, superficial infection, hyperviscosity of the blood, eating problems, blood incompatibility)

and type of jaundice (*icterus praecox* and *icterus gravis*, with no reports of prolonged jaundice). The obtained data are presented with tables and figures. Statistical analysis was performed using SPSS software system, along with the chosen level of significance of $p=0.05$. Comparison of variables was tested by χ^2 -test.

Results

The study included 800 infants: 198 (24.8%) jaundiced and 602 (75.8%) non-jaundiced. The research covered some of the general characteristics of the jaundiced patients, then the characteristics of mothers of observed children as well as possible causes and types of pathological jaundice in newborns.

General characteristics of newborns

The general characteristics of the observed jaundiced patients are gender, birth weight and gestation. The study included 399 male and 401 female newborns, 100, i.e. 98 of whom were jaundiced, respectively. Nearly identical values were obtained from the comparison of the incidence of jaundice in newborns according to sex: the share of male jaundiced newborns in the total number of male infants was 25% and the share of female jaundiced infants in the total number of female infants was 24%. Figure 1 shows the share of hypotrophic jaundiced newborns in the total number of hypotrophic newborns as well as the same share for eutrophic newborns. Even though jaundice is more common in hypotrophic newborns, a statistically significant difference was not detected ($p>0.05$). The study included mature infants (gestational age 37–42 weeks) and 27 preterm infants (gestational age 35 and 36 weeks), none of whom had additional com-

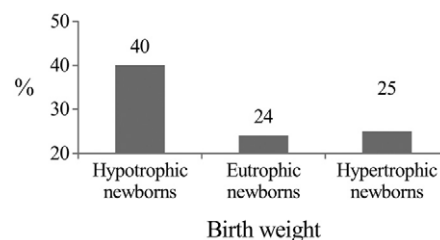


Fig. 1. Incidence of jaundice due to birth weight.

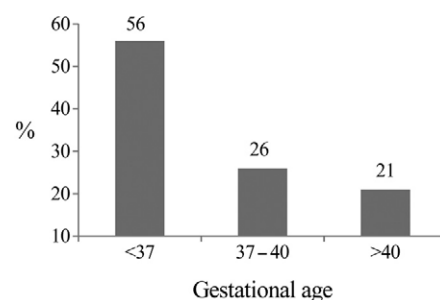


Fig. 2. Incidence of jaundice due to gestational age.

TABLE 1
INFLUENCE OF THE BIRTH WEIGHT, GESTATION AND BIRTH ORDER ON THE APPEARANCE OF JAUNDICE

	Number of newborns			χ^2	p
	With jaundice	Without jaundice	Total		
Birth weight					
Hypotrophic	6	9	15	1.91	>0.05
Eutrophic	170	526	696		
Gestation					
<37 weeks	15	12	27	11.63	<0.05
37–42 weeks	120	350	470		
Birth order					
First	98	243	341	1.89	>0.05
Second	65	208	273		

plications. Figure 2 shows the share of jaundiced newborns in the total number of infants of the same gestational age, divided into three groups according to gestational age. The obtained results show a higher incidence of jaundice in preterm gestational age of 35 and 36 weeks, with a statistical significance of $p < 0.05$.

Table 1 shows the relative frequency of jaundice in newborns born in a specific birth order. Jaundice is most common in first-born infants. Statistical analysis of the data has not shown a correlation between the onset of jaundice and birth order of the infants ($p > 0.05$).

Characteristics of mothers of observed newborns

The characteristics of mothers observed in the study included maternal age, residence, complications during pregnancy and during labor as well as the mode of delivery.

Table 2 shows the observed pregnancy complications: maternal infection, eclampsia, diabetes mellitus and gestational diabetes as well as other chronic diseases of the mothers. Various data on the maternal infections during pregnancy were collected from medical records. The states and causes mentioned therein included colpitis, *U. urealyticum*, *M. hominis* and *E. coli*. Other reported chronic illnesses included hypothyroidism, epilepsy and thrombophilia. The results are presented for the two groups: mothers of jaundiced newborns and mothers of

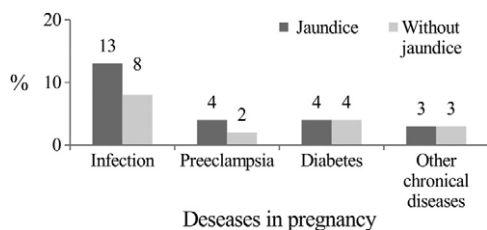


Fig. 3. Incidence of jaundice due to diseases of mother during pregnancy.

TABLE 2
MOTHER'S COMPLICATIONS DURING PREGNANCY AND NEWBORN'S JAUNDICE

	Number of newborns			χ^2	p
	With jaundice	Without jaundice	Total		
Infection in pregnancy					
With	25	47	72	4.83	<0.05
Without	167	556	723		
Preeclampsia					
With	8	13	21	2.29	>0.05
Without	184	590	774		
Diabetes mellitus or gestational diabetes					
With	8	26	34	0.01	>0.05
Without	184	577	761		

TABLE 3
CONNECTION OF NEWBORN JAUNDICE WITH THE MODE OF DELIVERY AND COMPLICATIONS DURING THE LABOR

	Number of newborns			χ^2	p
	With jaundice	Without jaundice	Total		
Mode of delivery					
Spontaneous	77	271	348	3.86	<0.05
Stimulated or induced	88	195	283		
Amniotic fluid					
Green or meconial	7	40	47	3.86	>0.05
Normal	185	563	748		
RVP					
With	27	44	71	8.19	<0.05
Without	165	559	724		
Complications with umbilical cord					
With	61	165	226	3.86	>0.05
Without	131	438	569		

non-jaundiced newborns. Figure 3 shows the share of jaundiced newborns and maternal infections in the total number of newborns whose mothers reported some of these pregnancy complications. The same share is shown for non-jaundiced infants. The same share was calculated for jaundiced and non-jaundiced infants whose mothers reported eclampsia, diabetes mellitus or gestational diabetes or any other chronic disease as a pregnancy complication. Statistical analysis of the data showed a statistically significant difference between jaundice onset and maternal infection during pregnancy ($p < 0.05$). Table 3 includes the following complications dur-

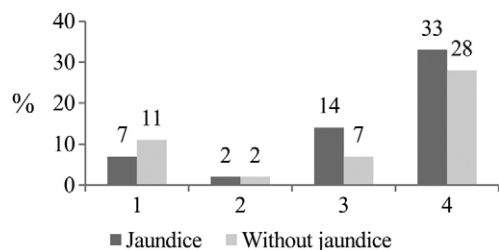


Fig. 4. Incidence of jaundice due to complications during birth, 1 - Amniotic fluid changes, 2 - Oligopoli hidramnion, 3 - RVP, 4 - Umbilical cord.

ing childbirth: amniotic fluid changes (green and meconium amniotic fluid), oligohidramnion/polyhydramnion, RVP (premature rupture of the membranes) and the wrapping of the umbilical cord around the body/true knot of the umbilical cord. The most common complication is the wrapping of the umbilical cord around the body. Results are presented for two groups as well: jaundiced and non-jaundiced infants. Figure 4 shows the share of jaundiced, i.e. non-jaundiced newborns per type of birth complication. Statistical analysis proved a correlation between the onset of jaundice and RVP ($p < 0.05$).

Figure 5 shows the dependence of the onset of jaundice on the mode of delivery. Childbirth may be spontaneous, by caesarean section or by inducing or stimulating labour. Children born by stimulating or inducing labor formed one study group. The diagram shows the share of jaundiced and non-born by a certain delivery mode in the total number of births of jaundiced or non-jaundiced children. The χ^2 -test revealed a statistically significant difference between the onset of jaundice and mode of delivery: jaundice is more common in newborns that were

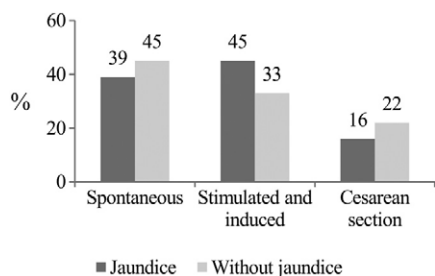


Fig. 5. Incidence of jaundice due to mode of delivery.

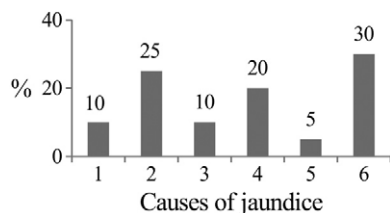


Fig. 6. Causes of jaundice in newborns. 1 - systemic infection, 2 - superficial infection, 3 - hyperviscosity syndrome, 4 - eating problems, 5 - blood incompatibility, 6 - unknown.

born by stimulating or inducing labor than in those born spontaneously ($p < 0.05$).

Types and causes of jaundice

The possible causes of jaundice as mentioned in the medical records include systemic infection, superficial infection, hyper viscosity syndrome, eating problems and blood incompatibility. The term systemic infection refers to the diagnosed perinatal infections in infants. Superficial infections include impetigo, nasal congestion and the administering of antibiotics into the eye. Plethoric infants and those with the haematocrit level exceeding 65% were placed in the category of hyper viscosity of the blood. Eating problems were diagnosed in infants who lost more than 5% of the body weight in their first days. All cases of blood incompatibility included in the study were O-A.

Figure 6 shows the frequency of observed causes of jaundice in newborns. Of the observed causes, 30% are unknown. Jaundice may be divided into early, severe and prolonged. The study found no reports of prolonged jaundice, whereas 35% of infants had an early onset of jaundice and 65% had severe jaundice.

Discussion

The study included 800 infants born in the final four months of 2011. The share of male jaundiced infants in the total number of male infants was 25%, and the share of female jaundiced infants in the total number of female infants was 24%. The study indicates that the share of male, i.e. female jaundiced infants in the total number of male, i.e. female infants (relative frequency) is the same. The result indicates that the occurrence of jaundice does not depend on the sex and that it is equally common in male and female newborns. A study conducted in California also found that the gender of newborns is not associated with the development of jaundice⁷. Infants were divided in three groups according to their birth weight: hypotrophic, eutrophic and hypertrophic newborns. Jaundice is most common in hypotrophic infants: of the 15 hypotrophic infants in the study, 6 (40%) were jaundiced. However, the statistical analysis of the data obtained showed that this is not significant. Upon examining literature Nonetheless, a research showed that the occurrence of jaundice in newborns with a low birth weight is linked to low gestational age⁸. The share of jaundiced newborns of gestational age of fewer than 37 weeks in the total number of infants of the same age is 56%. The share of jaundiced infants of gestational age of 37-40 and of over 40 weeks was 26% and 21%, respectively. The statistical analysis of data did not show a significant difference between the occurrence of jaundice in hypotrophic and eutrophic newborns. As regards the mothers, the study recorded the birth order of the 758 infants included in the study. Most of the infants were from the first pregnancy - 307 of them 91 (30%) of whom were jaundiced, making it the highest percentage in comparison with the relative frequencies of jaundice onset in

newborns of other birth orders. The dependence of the onset of jaundice on the birth order was observed in 754 mothers and infants. Most of the infants with jaundice were born from the first pregnancy – 98 of them (29%). Data processing showed that there was no statistically significant difference between the birth or pregnancy order and the occurrence of jaundice. A study conducted in Israel obtained the same results regarding the connection between birth order and jaundice onset⁹.

The study also recorded certain characteristics of the mothers, such as the mode of delivery and complications during pregnancy and childbirth. The observed complications during pregnancy include genitourinary tract infection, preeclampsia, diabetes mellitus and gestational diabetes and other chronic diseases such as hypothyroidism, epilepsy and thrombophilia. Statistical analysis of the data showed a connection between jaundice and infections of the urinary tract of the mother. Possible birth methods include spontaneous, stimulated, induced and caesarean section. Of the jaundiced infants included in the research, 77 (39%) were born by a spontaneous vaginal delivery, 70 (36%) by stimulation, 18 (9%) by induction and 32 (16%) by caesarean section. Of the jaundiced infants, 271 (45%) were born by a spontaneous vaginal delivery, 154 (26%) by stimulation, 41 (7%), by labour induction, and 130 (22%) by caesarean section. Most of the infants, both jaundiced and non-jaundiced, were born by a spontaneous vaginal delivery. When considering only the newborns born by stimulation or induction, it is evident that the relative frequency of jaundiced newborns is higher than the relative frequency of non-jaundiced newborns. Statistical data processing proved a correlation between the onset of jaundice and the mode of delivery: jaundice is common in newborns born by stimulation or labor induction. The literature revealed various data:

several studies failed to prove the impact of mode of delivery on the occurrence of jaundice^{8,10,11}. Of the complications during birth, the study recorded green amniotic fluid, meconial amniotic fluid, oligohydramnion or polyhydramnion, wrapping of the umbilical cord around the body and RVP. Statistically significant differences were found in the onset of jaundice and RVP. The study included a certain number of jaundiced infants as well, with the aim of observing some of the possible causes of this type of jaundice. Perinatal infections were recorded in 18 infants, which allows for the assumption that it may be a possible cause of jaundice in 10% of newborns¹². Of the infants observed in the study, 50 were found to have impetigo-like skin changes or nasal congestion, some of whom had received antibiotics into the eye. These were included in the group of infants with superficial infections, which are the possible cause of jaundice in 25% of cases. O-A incompatibility was observed in 10 (5%) jaundiced infants, and hyper viscosity syndrome in 19 (10%). The study included 41 newborns that lost more than 5% of their birth weight in their first days, making 20% of the total number of jaundiced newborns. There were no cases of prolonged jaundice, whereas in 35% of the cases jaundice had an early onset and in 65% it was severe.

Conclusion

The study covered a large number of potential factors that could influence the onset of jaundice in newborns. Jaundice in the perinatal period is associated with the gestational age, maternal infections during pregnancy, RVP and the mode of delivery.

REFERENCES

- MARDEŠIĆ D, Pedijatrija (Školska knjiga, Zagreb, 2003).
- MARTIN CR, CLOHERTY JP, Neonatal hyperbilirubinemia. In: CLOHERTY JP, EICHENWALDEC, STARK AR (Eds) Manual of neonatal care (Lippincott Williams and Wilkins, Philadelphia, 2007).
- DRAŽANČIĆ A, Porodništvo (Školska knjiga, Zagreb, 1999).
- KUVAČIĆ I, KURJAK A, ĐELMIŠ J, Porodništvo (Medicinska naklada, Zagreb, 2009).
- OMIGBODUN AO, Int J Gynecol Obstet, 40 (1993) 235.
- SAHIN HG, Arch Gynecol Obstet, 280 (2009) 889.
- KUZNIEWICZ MW, J Pediatr, 153 (2008) 234.
- LANGE AP, SECHER NJ, WESTERGAARD JG, SKOVGARD I, Lancet, 1 (1982) 991.
- SEIDMAN DS, ERGAZ Z, PAZ I, LAOR A, REVEL – VILK S, STEVENSON DK, GALE R, J Perinatol, 19 (1999) 564.
- BEAZLEY JM, WEEKES AR, Br J Obstet Gynaecol, 83 (1976) 62.
- BEAZLEY JM, ALDERMAN B, Br J Obstet Gynaecol, 82 (1975) 265.
- MILAS V, MILAS J, PUŠELJIĆ S, GARDAŠANIĆ J, VUKOVIĆ D, MILAS J, Coll Antropol, 28 (2004) 2.

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NEKONJUGIRANE PATOLOŠKE ŽUTICE U NOVOROĐENČADI

SAŽETAK

Hiperbilirubinemija u novorođenčadi je pojava povišenih vrijednosti bilirubina u krvi. Ona može biti fiziološka ili patološka. Ako je koncentracija nekonjugiranog bilirubina u krvi visoka, on prolazi krvno moždanu barijeru i razvija se bilirubinska encefalopatija s ozbiljnim posljedicama po dijete. Cilj rada je ispitati učestalost patološke nekonjugirane žutice u novorođenčadi i povezati ju s nekim epidemiološkim varijacijama (medicinskim, socijalnim, demografskim) te dokazati povezanost učestalosti indirektno žutice s načinom poroda (stimulacijom i indukcijom). Istraživanjem je obuhvaćeno 800 novorođenčadi: 198 njih je imalo, a 602 nije imalo žuticu. Statističkom analizom dokazana je povezanost pojave žutice u novorođenčadi i slijedećih parametara: gestacijske dobi, infekcije majke za vrijeme trudnoće, preranog prsnuća plodovih ovoja, te načina poroda.