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Original Article

Analysis of Pathology in Premature Infants in Obstetrics and Gynecology Clinic at St George University Hospital, Plovdiv between 2013 and 2015

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Abstract

Introduction: Premature birth is now one of the most profound prenatal problems worldwide because of the high morbidity and mortality it is associated with at the beginning of life. Advances in prenatal medicine over the past decades have led to a significant improvement of neonatal survival in risk groups of newborns. Infants of gestational age of 22-25 weeks represent the greatest medical, social, and ethical dilemma in neonatology. Most of these newborns need intensive care to survive, and most infants born between 28 and 32 weeks of gestation require special care. Those born 34 to 36 weeks' gestation also have higher rates of short-term morbid premature birth-related conditions such as respiratory distress syndrome (RDS) and intraventricular hemorrhage (IVH) than their peers born at term.

Aim: To carry out an analysis of morbidity during the neonatal period in premature babies.

Materials and methods: A retrospective triennial study was conducted on 598 premature newborns.

Results: The results of the study show that morbidity rate in premature born infants is high. The most frequent reasons for admission to the neonatal intensive care unit are the other forms of respiratory distress syndrome (45%). Respiratory distress syndrome (RDS) was observed in 23.41% of the prematurity, 10.7% of them were suspected of having other pathology, and 20.9% of premature neonates manifested no complications in the neonatal period. There was a significant difference in the diagnosis of newborns after birth (p=0.0001, r=0.58), with the newborns with RDS demonstrating the most complications in the neonatal period.

Conclusions: The conclusions to be drawn from the analysis of the data are as follows: there is wide comorbidity in the prematurity of RDS. Lower gestational age strongly correlates with the development of RDS. If no corticosteroid therapy is administered the risk of developing hyaline membrane disease increases. There is extremely high probability of neonatal mortality in children with hyaline membrane disease. There is significant difference between the primary diagnosis and the condition of the child at discharge from the medical establishment. Adequate and specialized prenatal care is essential when trying to reduce the incidence of preterm birth.

Keywords

morbidity, preterm birth, prematurity, RDS

INTRODUCTION

Despite the substantial advances that have been made in recent years in prenatal care, there has been a gradual and steady increase in preterm births even in developed countries.[1]

Preterm births have become now a considerable public health problem across the world because of the significant morbidity and mortality they are associated with.[2,3] The advances in prenatal medicine over the past decades have led to a remarkable improvement in the neonatal survival in risk groups of newborns. New methods and techniques of continuous respiratory resuscitation, artificial pulmonary ventilation, and intensive therapy have been introduced. Survival have increased for infants at low gestational age and with low birthweight.[4] The accepted limit of viability decreases progressively to 26 gestational weeks, 24 gestational weeks, 22 gestational weeks. But at the same time, the incidence of survivors with permanent disabilities remains constant.[4]

Introduction of antenatal corticosteroid prophylaxis and postnatal surfactant treatment, nasal and high frequency ventilation significantly improved the chance of life for very low and extremely low birthweight infants.[5]

Infants of gestational age of 22-25 weeks represent the greatest medical, social and ethical dilemma in neonatology.[6] Most of these newborns (born earlier than 28 weeks of gestation), require intensive care to survive, and most infants born between 28 to 32 weeks of gestation require special care.

Children born from 34 to 36 gestational weeks also experience elevated rates of short-term morbidity associated with premature birth, such as RDS and intraventricular hemorrhage, rather than their term mature peers.[7] In the long term, these children have inferior results in the development of the nervous system, weaker school performance, and increased risk of cerebral palsy.[8] Globally, they have the greatest impact on public health and this is essential for the planning of services, care and the need for special attention for moderately premature babies.[9]

Respiratory distress syndrome is the most common cause of death for premature babies.[10] Even those who survive are characterized by a high risk of developing cerebral palsy, subsequent problems during the educational process and respiratory disorders.[11]

AIM

The purpose of this study was to perform a morbidity analysis of the neonatal period in premature babies.

MATERIALS AND METHODS

A retrospective study was conducted using the information for all preterm births in St George University Hospital for the period of 2013-2015. Five hundred ninety eight (598) premature newborns were studied, which are conditionally divided into 4 groups:

Group 1 – premature neonates with RDS;

Group 2 – premature neonates with other forms of RDS – conditions that manifest themselves with symptoms of respiratory failure, which are not due to hyaline membrane disease (HMD);

Group 3 – premature neonates with other pathology – this includes all conditions not directly related to RDS and other forms of RDS, namely, intra-amniotic infection (IAI), congenital malformations, neonatal jaundice, neonatal skin infection, transient neonatal hypoglycemia, neonatal polycythemia, cardiovascular disorders, neonatal aspiration, non-infectious diarrhea, etc.;

Group 4 – premature neonates without complications in the neonatal period.

A documentary method was used primarily, with primary data on pre-term infants collected from the medical case histories, maternal discharge summaries and the newborn child's discharge summaries. A logical unit of observation was any premature child (born before 37 weeks of gestation). The study excluded cases involving infants with low birth weight, but with a gestational age of 37 or older and ante- or intranatal death.

Based on gestational age, premature births were divided into "late and moderately preterm neonates" – newborns born from 32 to 37 weeks of gestation, "very preterm neonates" – from 28 to 32 weeks, and "extremely preterm neonates" – born before turning 28 weeks of gestation. Low birth weight babies can be further classified as low birth weight (LBW) – 1500 to 2499 g, very low birth weight (VLBW), which includes infants under 1500 grams and preterm extremely low birth weight (ELBW) – all newborns born under 1000 grams.

The obtained data were analysed using correlation analyses (Pearson, Spearman coefficient), frequency distribution, linear regression analysis, nonparametric dispersion analysis (Mann-Whitney test), and chi-square test. Analyses were performed using SPSS software version 23.0. $P<0.05$ was considered statistically significant.

The study was approved by the Ethics Committee of the Medical University of Plovdiv (No R-1231/26.04.2018).

RESULTS

Five hundred ninety-eight premature neonates were included in the study. The mean gestational age of the studied contingent was 33.51±2.66 weeks of gestation with the minimum gestational age being 24 and the maximum 36 (**Fig. 1**). The highest rate was in infants with "late and moderate prematurity" (32-37 weeks) – 73.1%, "very premature neonates" (28-32 weeks) were 22.74%, and with "extreme prematurity" (<28 weeks) is 4.18%. However, when analyzing prematurity by weight, the following differences were noted – with extremely low birth weight (ELBW) were 6%;

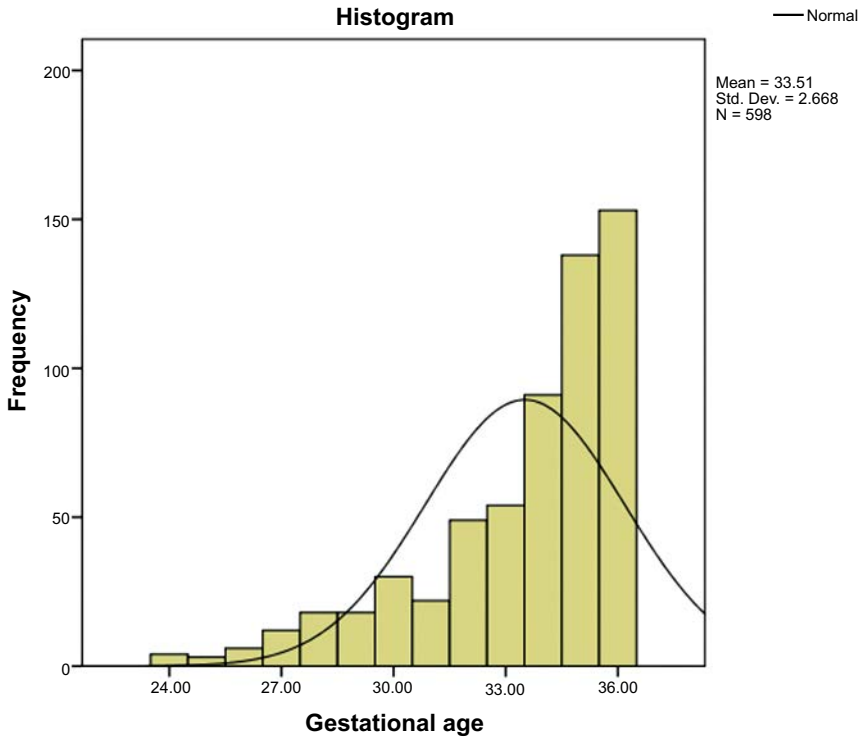

Figure 1. Mean gestational age of studied contingent.

very low birth weight (VLBW) rates were 13.7%; newborns with low weight from 1500 to 2499 g were 80.2%.

The reasons for admission to the neonatal intensive care unit with the highest incidence were the other forms of respiratory distress syndrome (45%). These included conditions that manifested with symptoms of respiratory failure that are not hyaline membrane disease-related. Respiratory distress syndrome (RDS) was observed in 23.41% of the premature infants, 10.7% of them had other pathology, and 20.9% of premature neonates had no complications in the neonatal period (**Fig. 2**).

There was high morbidity among premature neonates. In the prematurity with RDS, extensive comorbidity was observed (**Fig. 3**). HMD was observed in 57.14%; 31.43% had intraventricular neuropathic hemorrhage, 27.85% had congenital and/or aspiration pneumonia, 20.71% – cerebral edema, 11.42% had an intra-amniotic infection, 10.71% had pulmonary hemorrhage, and 7.14% had neurological symptoms. Concomitant pathology in the infants with other forms of RDS was predominantly associated with the intra-amniotic infection – 14.87%, neonatal aspiration – 4.83%, 4.43% anemia of prematu-

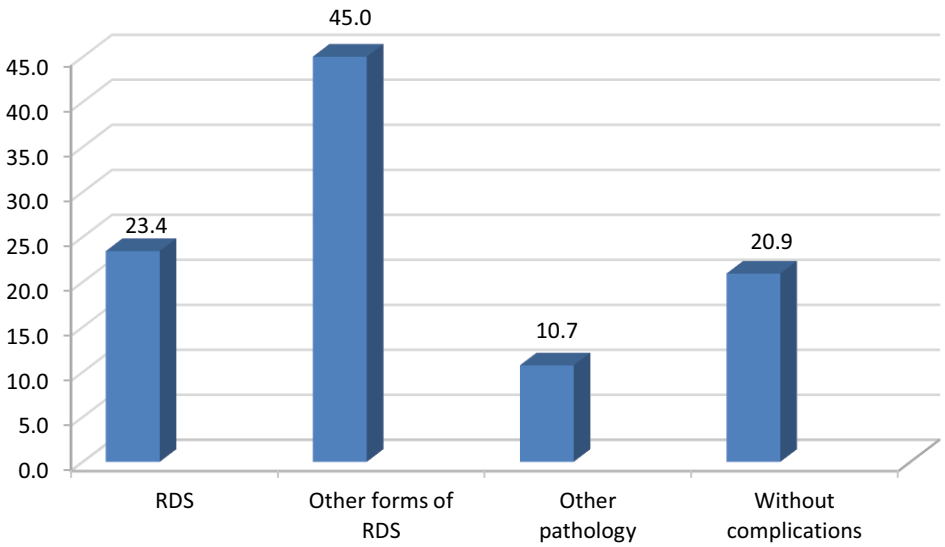

Figure 2. Distribution of the prematurity by pathology in the neonatal period.

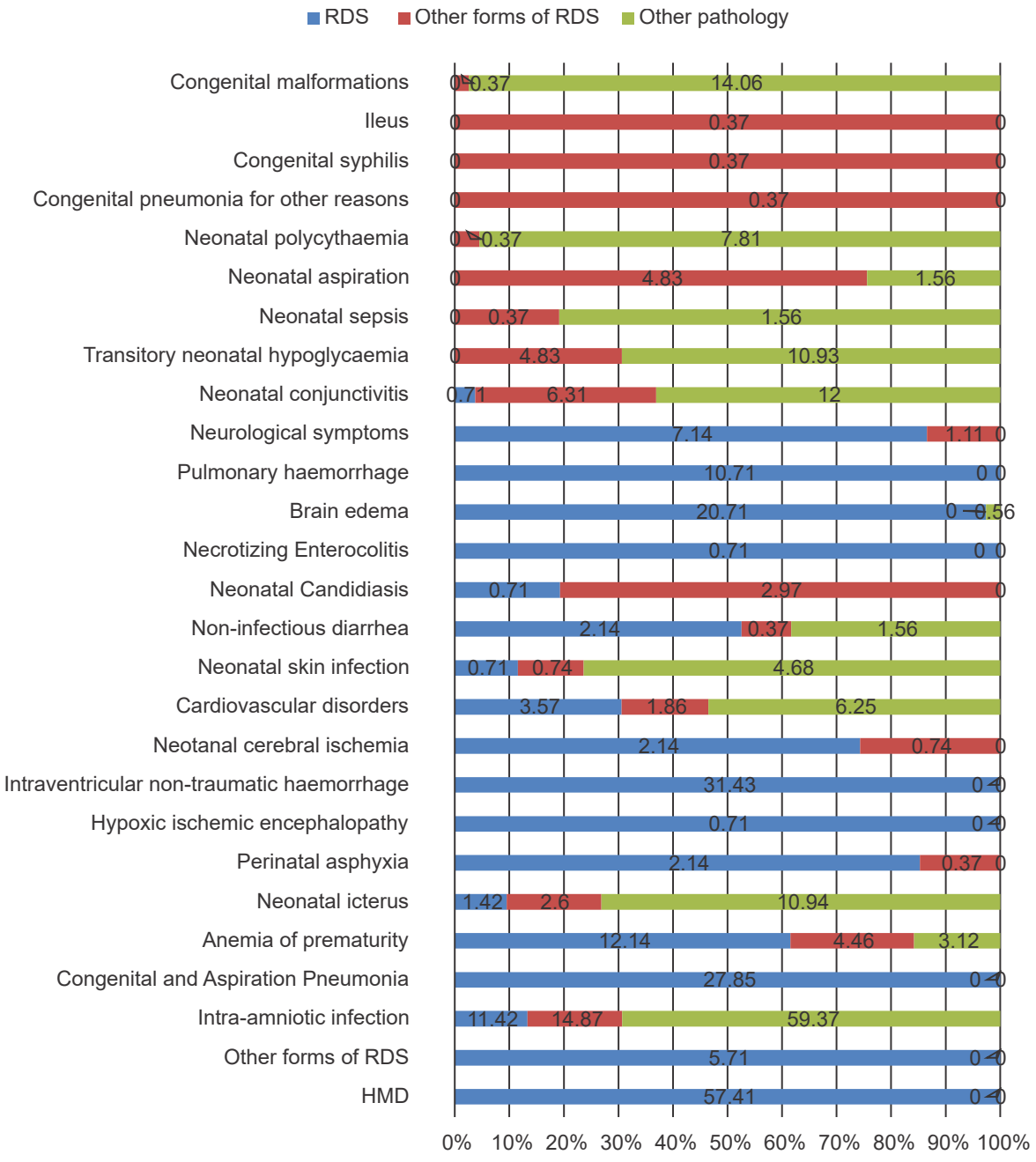

Figure 3. Morbidity in premature newborns.

rity and 4.83% transient neonatal hypoglycemia – 4.83%. The leading cause for admission of the premature infants to a neonatal intensive care unit in the group with other pathology was the IAI – 59.37%. It should be noted that most of the newborns had multiple pathology, which included several respiratory system disorders.

There was a statistically significant correlation between maternal vaginal infection during pregnancy and intra-amniotic infection in preterm infants (p=0.00005, r=0.16). In 62.8% of women, no treatment for vaginal infection was administered and 48.2% of them reported extra genital infection. 13.8% of the mothers of newborn infants with IAI were not systematically monitored by a specialist during pregnancy. An extremely large percentage of the premature births with IAI (97.9%) needed resuscitation immediately after birth (p=0.003, r=0.12).

There was a significant difference in the diagnosis of newborns after birth (p=0.0001, r=0.58), with the most complications in the neonatal period occurring in the newborns with RDS. In the linear regression analysis we found correlation between gestational age and number of pathological syndromes and conditions at birth (multiple R=0.593). When the gestational age decreases, the number of complications and accompanying pathology increases (Sig F=0.0001, Sig T=0.0001). (**Fig. 3**)

The highest comorbidity was reported in the ELBW

preterm neonates group – 19.4% of them had at least two pathological conditions, 19.5% had three, and 61.1% had four or more. The pathology in the newborn increases (p=0.0001, r=0.51) with birth weight.

A comparative analysis was performed between the study groups versus the gestational age, birth weight and birth rate, number of days in the neonatal intensive care unit, artificial pulmonary ventilation, oxygen-free adaptation, and Apgar scores in 1st and 5th minute (**Table 1**). The most unfavourable indicator was the RDS group.

As shown in **Table 1**, the lower gestational age is clearly associated with an increased risk of developing RDS (p=0.0001, r=0.61). These children had the longest stays in hospital (33.64±13.26) and needed artificial pulmonary ventilation the longest (8±6.50). It took more time for the premature infants with RDS to adapt without oxygen

Table 1. Comparative analysis between the groups of surveyed premature newborns

	Mean	x±SD	Min	Max
RDS				
Gestational age	30.34	2.85	24	36
Weight at birth	1402.00	494.85	590	2480
Height at birth	38.69	4.64	26	46
Number of days in hospital	33.64	13.26	8	88
Artificial pulmonary ventilation	8.00	6.50	1	47
Oxygen-free adaptation on ... day	18.88	9.19	5	62
APGAR – 1 min	5.06	2.28	1	9
APGAR – 5 min	7.68	1.67	3	10
Other forms of RDS				
Gestational age	34.04	1.75	28	36
Weight at birth	2006.54	331.32	900	2480
Height at birth	43.75	2.50	33	47
Number of days in hospital	15.23	8.21	6	51
Artificial pulmonary ventilation	3.65	6.59	1	40
Oxygen-free adaptation on ... day	4.64	4.20	1	51
APGAR – 1 min	7.62	1.08	3	9
APGAR – 5 min	9.08	0.75	7	10
Other pathology				
Gestational age	34.47	1.79	26	36
Weight at birth	2076.41	279.37	1020	2480
Height at birth	43.83	2.40	33	46
Number of days in hospital	14.96	8.73	1	41
Artificial pulmonary ventilation	1.5	0.70	1	2
Oxygen-free adaptation on ... day	3.33	1.95	1	9
APGAR – 1 min	7.61	1.58	1	9
APGAR – 5 min	9.13	1.33	1	10
Without complications				
Gestational age	35.43	0.81	30	36
Weight at birth	2371.68	81.97	2090	2480
Height at birth	45.62	0.8	43	47
Number of days in hospital	4.33	0.96	4	11
Artificial pulmonary ventilation	-	-	-	-
Oxygen-free adaptation on ... day	-	-	-	-
APGAR – 1 min	8.31	0.75	6	9
APGAR – 5 min	9.58	0.56	8	10

(18.88±9.19 days on average). 57.14% of the newborns with RDS had auscultatory and X-ray findings in HMD. In our study, the outcome in 44.44% of the premature infants with HMD was lethal, which is 73.4% of all premature deaths in the neonatal period. Widespread comorbid pathology was found in the cases of graduates: 87.75% of them had intraventricular non-traumatic hemorrhages, 59.18% had cerebral edema, pulmonary hemorrhage was observed in 30.61%, 20.41% had congenital and aspiration pneumonia, and 4.08% had cardiovascular disorders. Fifty-three percent of the cases were premature births up to 28 gestational weeks. We found a statistically significant correlation between gestational age and RDS. The mean gestational age of neonates with HMD was 29.51±2.57, of infants with RDS – 30.34±2.85, and 34.04±1.75 in other forms of RDS. The probability of lethal outcome in infants with HMD was extremely high (OR=31.01 95% CI, 15.35-62.69) (p=0.0001, r=0.46)

Extremely low birth weight infants account for the highest percentage of deaths (49%), followed by VLBW (26.5%). The mortality rate of the low birth weight infants (1500–2499 g) was 24.5%.

It is worth noting that newborns delivered via caesarean section were at a higher potential risk of developing RDS. The probability of this increased almost twice (p=0.001, r=-0.14) (OR=1.92 95% Cl, 1.31-2.82).

No corticosteroid therapy was received by 35.8% of the infants with HMD. The reasons for this were the short time from the hospital admission of these women to the actual delivery and the complete failure to administer such a preventive therapy. The risk for developing HMD rose twofold in the absence of corticosteroid prophylaxis (p=0.0001, r=0.15) (OR=2.38 95% CI, 1.46-3.87). On the other hand, missing corticosteroid therapy was followed by a higher rate of exogenous surfactant which in many cases increased the risk for the newborn and incurred extremely high treatment costs.

We showed that the probability of exogenous surfactant increased 2.5 times in preterm pregnancy with absent corticosteroid therapy (p=0.0001, r=-0.18) [OR=2.46 95% Cl, 1.65-3.66). One hundred twenty-six (90%) children with RDS were given exogenous surfactant, compared to 5 (1.9%) of the group with other forms of RDS. With a single application were 77 infants, and with a multiple – 44 newborns from group RDS (**Fig. 4**).

Significant difference was found between the primary diagnosis and the condition of the child at hospital (p=-0.0001, r=-0.55) (**Fig. 4**). The smallest percentage of clinically healthy patients was observed in the group with a RDS of 25%. This group also had the highest percentage of newborns transferred to other treatment facilities – 15.05%, followed by newborns with other pathology – 13.11%, and other forms of RDS – 2.97%.

DISCUSSION

A number of studies have shown an increased risk of morbidity in preterm infants compared to those infants born at term. Morbidity is mainly associated with developing respiratory distress syndrome[12], bronchopulmonary dysplasia, retinopathy, intraventricular hemorrhage, periventricular leucomalation, and cerebral palsy. However, studies are not comparable due to differences in the diagnostic approach and level of care for the premature in the different countries.[13,14] In our study there is a wide comorbidity, the ne-

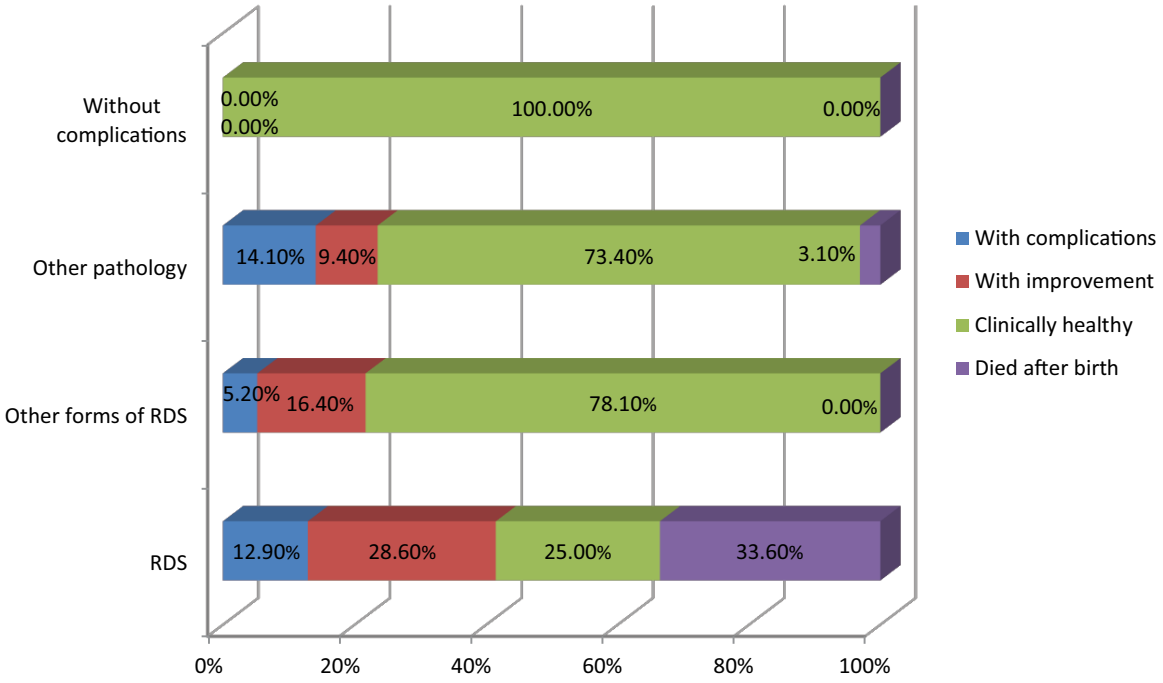

Figure 4. Condition of the premature infants at discharge.

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wborns with RDS are with the most complications in the neonatal period. When gestational age decreases, the number of complications and accompanying pathology increases. In two-thirds (79.1%) of newborns there is a variety of pathology requiring special care. The results of the study show that all premature organs and systems are affected due to their immaturity, but the respiratory complications are the ones that are most commonly observed. The highest comorbidity was reported in the ELBW preterm neonates group – 19.4% of them had at least two pathological conditions, 19.5% had three, and 61.1% had four or more. With birth weight, the pathology in the newborn increases (p=0.0001, r=0.51). In the long term, these complications are associated with an increased risk of mortality and chronic problems. This confirms Yankova's claim that these premature infants represent the greatest medical, social and ethical dilemma in neonatology.[6]

Hyaline membrane disease (HMD) and respiratory distress syndrome (RSD) are respiratory complications in premature babies as a result of premature birth. This is due to a shortage in the synthesis of surfactants in combination with the structural immaturity of the lungs.[15] Hyaline membrane disease affects 1% of premature neonates in the world and is the leading cause of death in this patient population.[16] The outcome in 44.44% of the HMD prematurity in our study is lethal. This is 73.4% of all premature deaths in the neonatal period. HMD and RDS are breathing complications in premature babies as a result of premature birth. RDS is the most common cause leading to death among premature neonates.[17] In a study by Mihaylova et al.[18] on the incidence of HMD in preterm infants, 25 out of 167 children developed HMD (15%), and 101 of them (60.5%) developed other forms of respiratory distress syndrome.

The longest stay in hospital was observed in the premature infants with the RDS. A statistically significant correlation between gestational age and RDS was found. The mean gestational age of neonates with HMD was 29.51±2.57, infants with RDS – 30.34±2.85, and infants with other forms of RDS – 34.04±1.75. The probability of lethal outcome in the infants with HMD is extremely high [OR=31.01 95% CI, 15.35-62.69). This raises the question of adequate and timely prenatal care, as well as the coverage and prevention of risk factors associated with preterm birth.

Extensive comorbid pathology was found in the cases with lethal outcome. ELBW infants account for the highest percentage of deaths (49%) followed by VLBW (26.5%).

The leading cause of admission of premature infants to neonatal intensive care unit in the group with other pathology was IAI (59.37%). In 51.1% of women whose newborns had IAI, vaginal infection was reported during pregnancy, with 62.8% of them receiving no treatment for vaginal infection and 48.2% reporting extra genital infection. 13.8% of the mothers of newborn infants with IAI were not systematically monitored by a specialist during pregnancy. The analysis of the results supports the findings of Ouattara A et al.[18] that lack of prenatal care is a significant risk factor for preterm birth. Adequate prenatal care would reduce substantially the severity and consequences of preterm birth.

Mihaylova et al.[19] suggest that effective corticosteroid prophylaxis would shorten the length of stay in neonatal intensive care unit and consequently provide a better quality of life. This finding is confirmed in our study – the risk of developing HMD increases two-fold in the absence of corticosteroid prophylaxis. On the other hand, missing corticosteroid therapy is followed by higher exogenous surfactant use, which in turn increases the risk to the newborn and results in extremely high treatment costs. This is also demonstrated in a comparative analysis by Mihaylova et al.[19] The costs incurred for the HMD group are nearly twice as large as those with other forms of RDS and approximately more than three times the cost of the group without these complications.[20]

CONCLUSIONS

Based on the data analyzed, the following conclusions can be drawn.

1. There is a wide comorbidity in the prematurity of RDS.

2. Lower gestational age is strongly correlated with the development of RDS. Premature infants with RDS present with the most complications and accompanying pathology in the neonatal period.

3. Lack of corticosteroid therapy increases the risk of developing hyaline membrane disease.

4. The probability of neonatal mortality in children with hyaline membrane disease is extremely high.

5. There is significant difference between the primary diagnosis and the condition of the child at discharge from the medical establishment.

6. Adequate and specialized prenatal care is essential to reduce the incidence of preterm birth. They may also reduce the severity and effects of preterm birth.

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Анализ патологии недоношенных детей в клинике акушерства и гинекологии при университетской больнице Святого Георгия, Пловдив, с 2013 по 2015 годы

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Резюме

Введение: Преждевременные роды сегодня являются одной из самых серьёзных пренатальных проблем в мире из-за высокой заболеваемости и смертности, связанных с ранним возрастом. Достижения в пренатальной медицине за последние десятилетия привели к значительному увеличению выживаемости новорожденных из группы риска. Младенцы в возрасте 22-25 недель представляют собой самую большую медицинскую, социальную и этическую дилемму в неонатологии. Большинство этих новорожденных нуждаются в интенсивной терапии, чтобы выжить, и большинству детей, рождённых на сроке от 28 до 32 недель беременности, требуется особый уход. У тех, кто родился на сроке от 34 до 36 недель беременности, также была установлена более высокая частота краткосрочных патологических состояний, связанных с преждевременными родами, таких как респираторный дистресс-синдром (РДС) и внутрижелудочковое кровоизлияние (ВЖК) по сравнению с их доношенными сверстниками.

Цель: Проанализировать заболеваемость недоношенных в неонатальном периоде.

Материалы и методы: Ретроспективное трёхлетнее исследование было проведено среди 598 недоношенных детей.

Результаты: Результаты этого исследования показали, что заболеваемость недоношенных детей высока. Среди причин поступления в отделение интенсивной терапии новорожденных наиболее частыми являются другие формы респираторного дистресс-синдрома (45%). Респираторный дистресс-синдром (РДС) наблюдается у 23.41% недоношенных детей, у 10.7% из них – другая патология, а у 20.9% недоношенных детей не было осложнений в неонатальном периоде. Наблюдалась значительная разница в диагностике новорожденных после рождения (p=0.0001, r=0.58), при этом новорожденные с РДС демонстрировали наибольшее количество осложнений в неонатальном периоде.

Заключение: На основании анализа данных можно сделать следующие выводы: среди недоношенных детей наблюдается высокая коморбидность РДС. Низкий гестационный возраст сильно коррелирует с развитием РДС. Если не назначать кортикостероидную терапию, увеличивается риск развития болезни гиалиновой мембраны. Чрезвычайно высока вероятность неонатальной смертности у детей с заболеванием гиалиновых мембран. Существует значительная разница между первичным диагнозом и состоянием ребёнка при выписке из роддома. Адекватный и специализированный дородовой уход необходим для снижения частоты преждевременных родов.

Ключевые слова

заболеваемость, преждевременные роды, недоношенность, РДС