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Original scientific paper

Respiratory Distress Syndrome in Newborns of Gestational Age of over 32 Weeks

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A B S T R A C T

Albeit the aetiology of the respiratory distress syndrome (RDS) is well known, the paper shall demonstrate that the causes of RDS changed over the years 2006 and 2010. This retrospective study comprises analysis of the data collected from 60 newborns of over 32 weeks gestation with RDS in the Neonatal Intensive Care Unit at the Clinical Hospital Centre in Osijek. The focus of the paper lies in the difference in the incidence of RDS over two research periods (2006 and 2010), the most common and possible causes of RDS in newborns of over 32 weeks gestation as well as in the potential changes in the aetiology over the two research periods. An increase in the incidence of RDS was established in 2010, but it was statistically significant only for newborns of gestational age of 35 1/7 to 36 6/7 weeks. The most common cause of RDS in both research periods was sepsis, which decreased in its share in 2010, whereas the incidence of asphyxia and complications during pregnancy increased. The new potential cause in 2010 was maternal thrombophilia. The share of unknown causes of RDS decreased, although not significantly so. The results of the research indicate that the causes of RDS changed over the observed periods and that further research should focus on thrombophilia and other complications during pregnancy with the aim of reducing morbidity and improving neonatal outcomes as well as further reducing the incidence of RDS with unknown causes in newborns.

***Key words**: respiratory distress syndrome, newborn, sepsis, foetal hypoxia, perinatal asphyxia thrombophilia, complications during pregnancy*

Introduction

Acute respiratory distress syndrome (ARDS) is a life-threatening medical condition leading to inflammation and accumulation of fluid in the alveoli and lung interstitium. The syndrome may have onset at any age, including onset in newborns. The causes include pneumonia, pulmonary contusion, pulmonary fan injury and aspiration of gastric contents, inhalation of toxic gases, shock, sepsis, drugs, extensive blood transfusions, diabetic ketoacidosis, pancreatitis, disseminated intravascular coagulation and eclampsia[1–3]. The most common cause of ARDS is sepsis with share of around 40%[3].

The ARDS is characterized by the damaging or the disabling of the surfactant synthesis[4]. The main components of the surfactant are dipalmitoylphosphatidylcholine (lecithin), phosphatidylglycerol, apoproteins and cholesterol[5]. The surfactant reduces the surface tension between two different phases – air and fluid[1] in this case – and prevents transudation of fluid from the capillaries into the alveoli[6]. The synthesis of the surfactant depends on the pH, temperature and lung perfusion and is affected by hormones, the essential ones being glucocorticoids[4].

Other risk factors for RDS in newborns exist as well. They include male gender, mother's poorly controlled diabetes mellitus, second twin sibling, caesarean section delivery prior to the onset of labour, asphyxia, meconium aspiration, hereditary hyposurfactosis, mother's thrombophilia[5,7–12]. Most of the above factors cause intrauterine hypoxia or interfere with the action of glucocorticoids in the maturation of surfactant, leading to ARDS. Certain above ARDS factors are already known, but others – such as maternal thrombophilia – have just been discovered.

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Thrombophilia is a congenital or acquired blood clotting disorder that increases the risk of thrombosis (venous or arterial). Hereditary thrombophilia is a multigene illness that causes a lifelong increased tendency to form blood clots[13]. Thrombotic events often occur following the onset of the acquired factors of increased risk of thrombosis, which include trauma, surgery followed by a prolonged immobilization, obesity with the tendency for venous stasis, pregnancy and hormonal contraception[14]. During pregnancy, placental insufficiency may appear due to the thrombosis of the placental blood vessels, leading to recurrent miscarriage, fetal growth restriction, stillbirth, preeclampsia, placental abruption, intrauterine fetal death and premature birth[13,15,16]. It is not yet certain how the above leads to ARDS in newborns, but it likely occurs due to intrauterine hypoxia.

The aim of the research was to examine the incidence of RDS in infants of over 32 weeks gestation, to investigate the possibility that the incidence of RDS changed over the two research periods, to find the most common causes of RDS in affected newborns as well as to determine whether there had been changes in the aetiology over the research periods.

Subjects and Methods

Subjects

The retrospective research comprised the analysis of the data collected from newborns of over 32 weeks gestation, who had been diagnosed and treated at the NICU for the respiratory distress syndrome (RDS) at the University Hospital of Osijek during 2006 and 2010. The research included 60 children – 35 male and 25 female newborn infants – all of whom had been diagnosed with IRDS and ARDS. The research aimed at all possible causes of RDS, such as congenital malformations, sepsis, asphyxia, certain complications during pregnancy that could lead to RDS (gestational diabetes, chronic illness of the mother, such as thrombophilia, high blood pressure, hypo- or hyperthyreosis, acute infections during pregnancy) as well as complications during childbirth (preeclampsia, induced labour, multiple pregnancies) and unknown causes. Granting the fact that some newborns did have IRDS, each newborn with the clinical picture of RDS was included in the study. Albeit some children had more than one cause of RDS, the research focused on every possible cause and counted each of the causes separately.

Methods

The data were obtained from the medical records (children's books of admissions). The chosen and analyzed data included gestational age, gender, complications during pregnancy (acute infections, preeclampsia, gestational diabetes and chronic illnesses of the mother such as thrombofilia) and birth (multiple pregnancies, induced labor) as well as the diagnosis of the newborn admitted in the NICU. The data were analyzed separately for preterm infants of 32 to 36 6/7 weeks and separately for newborns of 37 and over weeks of gestation, followed by the analysis of the data of all newborns. Microsoft Office Excel 2007 was used for data processing. To test the statistical significance between samples χ^2-test with Yates' correction, Student t-test and the Mann-Whitney test were applied. Statistical hypotheses were tested at the level of significance for the risk of $p=0.05$. The difference between samples was considered significant if $p< 0.05$.

Results

RDS in premature infants

In 2006, the NICU at the University Hospital of Osijek admitted 377 newborns. The incidence of RDS among them (of 32 or over weeks of gestation) was 7.7%. The total number of newborns of between 32 and 36 6/7 weeks gestation was 100, and the number of preterm infants with RDS is 19 (i.e. 19%). The total number of admitted preterm newborns of 35 to 36 6/7 weeks gestation was 70, of whom 2 had RDS (3%). In 2010, the total number of admitted newborns was 374, of whom 31 had RDS (8.3%). The total number of admitted preterm newborns was 120, of whom 25 had RDS (20%); 90 preterm newborns of 35 to 36 6/7weeks gestation were admitted, of whom 9 had RDS (10%). In 2006, the majority of preterm infants diagnosed with RDS (89%) were born before week 36 of gestation, whereas in 2010 the share was 64% (Figure 1). There was no statistically significant change in the incidence of RDS up to week 36 of gestation ($\chi^2=0.03$ $p=0.862$ $p>0.05$), but the data collected for preterm infants over that gestational age showed that there was a change ($p=0.034$, $\chi^2=4.455$ $p<0.05$).

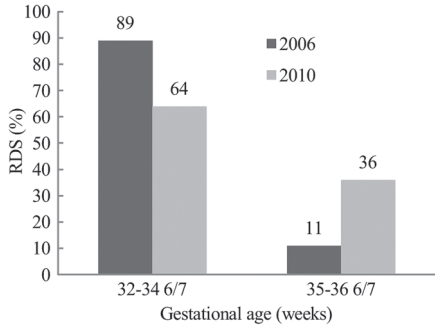

Fig. 1. Comparison of the incidence of RDS in preterm infants relating to gestational age in the two study periods.

In 2006, more male preterm infants were diagnosed with RDS (Table 1) – 74% – and the incidence in female infants amounted to 26%. In 2010 more female infants (56%) were diagnosed with the same condition (44% male). No statistically significant difference was established in the decrease in the number of male preterm infants with RDS in the observed periods ($\chi^2=0.36$, $p=0.548$ $p>0.05$), but there was statistically significant increase in the number of female preterm infants with RDS in 2010 in comparison to 2006 ($\chi^2=4.26$, $p=0.038$ $p<0.05$).

TABLE 1
COMPARISON OF INFANTS WITH RDS ACCORDING TO GESTATION AND GENDER IN THE TWO STUDY PERIODS

	2006		2010		Total	
	N	%	N	%	N	%
Prematures						
Gestation (weeks)						
32–32 6/7	3	10.3	7	22.6	10	16.7
33–33 6/7	5	17.2	4	12.9	9	15.0
34–34 6/7	9	31.0	5	16.1	14	23.3
35–36 6/7	2	6.9	9	29.0	11	18.3
Gender						
Males	14	48.3	11	35.5	25	41.7
Females	5	17.2	14	45.2	19	31.7
Total	19	65.5	25	80.6	44	73.3
Newborns						
Gender						
Males	6	20.7	5	16.1	11	18.3
Females	4	13.8	1	3.2	5	8.3
Total	10	34.5	6	19.4	16	26.7
Total	29		31		60	

N – number of cases

TABLE 2
ETIOLOGY OF RDS IN NEWBORNS IN THE TWO STUDY PERIODS

	Prematures				Newborns				Total			
	2006		2010		2006		2010		2006		2010	
Etiology of RDS	N	%	N	%	N	%	N	%	N	%	N	%
Sepsis	9	40.9	10	38.5	7	63.6	1	16.7	16	48.5	11	34.4
Asphyxia	7	31.8	7	26.9	1	9.1	2	33.3	8	24.2	9	28.1
Diseases in mother	3	13.6	7	26.9	1	9.1	2	33.3	4	12.1	9	28.1
Congenital anomalies	–	–	–	–	1	9.1	–	–	1	3.0	–	–
Unknown	3	13.6	2	7.7	1	9.1	1	16.7	4	12.1	3	9.4
Total	22		26		11		6		33		32	

N – number of cases

Among the causes of RDS in 2006 (Table 2) neonatal sepsis was the most common (41%), followed by asphyxia (32%) and complications during pregnancy (13%). The cause of RDS was reported as unknown in 14% of cases. In 2006 there were no cases of maternal thrombophilia (as one of complications during pregnancy) and congenital malformations related to RDS. In 2010 the most frequent cause of RDS was sepsis, followed by asphyxia and complications in pregnancy (diabetic fetopathy, chronic illness of mother such as thrombophilia). The cause was reported as unknown in 8%. New causes of RDS in 2010 according to the data collected for the research were thrombophilia (12%) and other chronic diseases of the mother (high blood pressure, hypo- or hyperthyroidisms, autoimmune diseases etc).Birth defects were not recorded in 2010. A statistically significant difference in the incidence of any of the causes in 2010 in comparison to 2006 ($p>0.05$) did not exist. Complications during pregnancy and during delivery are shown in Table 3 as well as even the least probable factors that affect the health of a newborn infant.

RDS in newborns

The most common cause of RDS in newborns in 2006 was sepsis with an incidence of 64%, followed by asphyxia, pregnancy complications and birth defects (laryngomalacia) with equal shares of 9%. Unknown causes were reported in 9% of the cases as well. In 2010, the most common cause of RDS in newborns was asphyxia (33%). Other causes, such as sepsis and pregnancy complications, had an incidence of 17% each and unknown causes were reported in 16% of the cases. Thrombophilia was seen as a new cause in 2010, occurring in 17% of the cases (half of all complications during pregnancy). No

TABLE 3
COMPLICATIONS IN PREGNANCY AND DELIVERY IN THE TWO STUDY PERIODS

	Prematures				Newborns				Total			
	2006		2010		2006		2010		2006		2010	
Complications	N	%	N	%	N	%	N	%	N	%	N	%
Acute infections	8	40.0	9	34.6	7	63.6	1	16.7	15	48.4	10	31.3
Preeclampsia	1	5.0	3	11.5	1	9.1		–	2	6.5	3	9.4
Gestational diabetes	3	15.0	1	3.8	1	9.1	1	16.7	4	12.9	2	6.3
Bleeding in pregnancy	2	10.0	2	7.7		–	1	16.7	2	6.5	3	9.4
Chronic diseases	–	–	5	19.2		–	1	16.7	–	–	6	18.8
Multiple pregnancies	1	5.0	2	7.7		–	–	0.0	1	3.2	2	6.3
Induced delivery	–	–	2	7.7		–	1	16.7	–	–	3	9.4
Without complications	5	25.0	2	7.7	2	18.2	1	16.7	7	22.6	3	9.4
Total	20		26		11		6		31		32	

N – number of cases

statistically significant difference was established in the incidence of any cause in 2010 in comparison to 2006 ($p>0.05$).

RDS in preterm infants and newborns

The analysis of the data recorded 29 cases of RDS in preterm infants (of over 32 weeks gestation) and newborns (37 and over weeks gestation) for 2006, making the incidence of RDS 7.7%. In 2010, 31 cases of RDS were recorded, making an incidence of 8.3%. The incidence of RDS increased in 2010 by 0.6%, but this was not statistically significant ($p=0.795$, $\chi^2=0.0153$).

In 2006 most newborns with RDS were born before week 37 of gestation. Albeit the difference in the data for the research period of 2010 is seen in a much higher percentage of newborns born in week 37 of gestation, no statistically significant change in the incidence was observed. Both in 2006 and 2010, more male newborns were diagnosed with RDS (Figure 2) – an incidence of 52% in male newborns and 48% in female newborns. The incidence of RDS in male newborns decreased and in female increased, but with no statistically significant differences ($p>0.05$).

The most common cause of RDS in newborns in 2006 (Figure 3) was sepsis, followed by asphyxia and complications during pregnancy. Unknown causes were reported in 12% of the cases and birth defects in 3%. In 2010, sepsis had the highest incidence, followed by asphyxia and complications during pregnancy. New causes in 2010 included thrombophilia and chronic illnesses of the mother. Almost no statistically significant changes were observed in the incidence of RDS causes, with the exception of thrombophilia, for which a statistically significant increase in 2010 in comparison to 2006 ($p=0.036$, $\chi^2=2.498$) was recorded.

The most common cause of RDS in newborns in the research periods 2006 and 2010 is sepsis (Figure 4), followed by asphyxia and complications during pregnancy. Unknown causes were reported in 11% of the cases, thrombophilia in 6% and birth defects in 1%.

Fig. 2. Comparison of the incidence of RDS in premature infants and newborns between sexes in the two study periods.

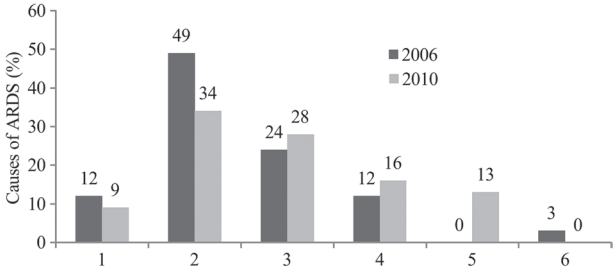

Fig. 3. Causes of RDS in premature infants and newborns in the two study periods, legends: 1– unknown, 2 – sepsis, 3 – asphyxia, 4 – complications in pregnancy, 5 – thrombophilia, 6 – birth defects.

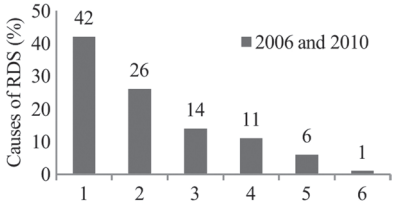

Fig. 4. Causes of RDS in all newborns in the two years (2006 and 2010), legends: 1 – sepsis, 2 –asphyxia, 3 – complications in pregnancy, 4 – unknown, 5 – thrombophilia, 6 – birth defects.

Discussion

This study has shown that the number of newborns diagnosed with RDS has not changed significantly in 2010 in comparison with situation in the year 2006. Out of the total number of newborns (377) of the gestational age of over 32 weeks who were hospitalized at the University Hospital of Osijek 2006, 29 (7.7%) newborn were diagnosed with RDS. In 2010, the number of newborns (374) diagnosed with ARDS did not increase much; it counted 31 (8.3%). The difference in the prevalence of 0.6% is not statistically significant. In the year 2006, the incidence of RDS among preterm newborns amounted to 19% while in 2010, it was about 20%; among newborns born between 35 and 37 week of gestation, this percentage was still high, precisely in 2010, it was 10%. Similar results can be found in the references[17,18].

Most children with RDS comprised by this study were born before week 37 of gestation. This estimate referred to both years. The corpus of children diagnosed with RDS was constituted mostly of preterm infants. Since there was no statistically significant difference in their frequency, the authors has drawn the conclusion that in the future, most children with ARDS can be expected to be born prior to week 37 of gestation. Also, there was no statistically significant increase in the number of preterm infants with ARDS born in the 36th and 37th week of gestation in 2010. This increase can be attributed to the reduction of the number of premature infants with RDS born detected prior to this period.

In 2006, most children with ARDS were boys (20–69%). The gender structure was similar in 2010 (16–52%). This corresponds with the findings in the references since they suggest that this syndrome mostly affects male children[4]. Taking account of the share of male children in both years, this figure was 60% (40% of girls); it means that there are 1.5 times more male children among newborns diagnosed with ARDS. This finding matches the results of the research of Skokić et al. in which they found that RDS occurs more frequently in male than in female newborns, with ratio of 1.5:1 in favor of boys[19,20]. In 2010, it came to a decrease in the share of male children with ARDS and consequently, to an increase in the share of female infants with ARDS. The reason for that lies in a reduced number of male preterm infants with RDS and in a rise of female infants having suffered from this syndrome. This can be explained by higher mortality of male children, especially premature ones.

Among the causes of RDS in newborns in the two study periods, the most common cause was sepsis, which complies with the data in the references showing the prevalence of this cause of 40%[3]. The reduction in the incidence of sepsis can be attributed to better perinatal care. Therefore, the prevention and treatment of neonatal sepsis remains the main way to reduce the incidence of RDS.

The second most common RDS cause was asphyxia, which is also confirmed in the references[20]. This cause gained importance in 2010. Complications in pregnancy appeared as the third most frequent cause of RDS, accounting for 14% of all causes of RDS in newborns in the two study periods. The complications included diabetic fetopathy and chronic diseases of mother. The connection between preeclampsia and RDS has been described in the references[21]. The influence of complications in pregnancy regarding the incidence of RDS increased in 2010, which resulted from an increased number of chronic illnesses of mother with respect to 2006. This increase can be connected with better diagnostic techniques (thrombofilia had not used to be diagnosed until the year 2007). In contrast, the influence of diabetic fetopathy diminished in this context in 2010. This can be attributed to better regulation of diabetes in pregnancy and the detection and treatment of gestational diabetes prior to its possible facilitation of newborn's complications. Our data show that inducted labor can be an RDS risk factor of RDS, which is an assertion stated in the references too[22].

Unknown cause of RDS in the two study periods made up 11% of cases. In 2006, such causes accounted for 12% of all RDS cases and in 2010 for 9% of all RDS cases; so obviously, the number of known detectable causes of RDS is increasing while the number of unknown ones is declining. Further analysis of this problem suggests that it is likely that the proportion of unknown causes of RDS will continue to fall.

Thrombophilia in mother was diagnosed in only 6% of all cases of RDS in newborns. It implies that it has only recently been regarded as a possible cause of RDS in newborns. The role of thrombophilia in the development of ARDS is still unknown, but it is thought that it leads to ARDS through intrauterine hypoxia. Testing of high-risk pregnant women for thrombophilia has not been conducted for a long time; precisely it has been taken advantage of since 2006, which is why the research there includes no cases of thrombophilia diagnosed in 2006. Since its introduction, this testing has discovered a statistically significant connection with the incidence of ARDS in newborns. Wide-spread testing of pregnant women may bring to a subsequent rise in the proportion of thrombophilia as a cause of ARDS while the unknown causes will be a rare occurrence in this light in the future. The birth defects in the study included laryngomalacia which is a very rare cause of ARDS. In the two study periods, birth defects accounted for only 1% of the total causes.

This study suggests that the causes of RDS have changed due to new findings regarding potential harmful factors in pregnancy, childbirth and neonatal diseases. It is necessary to proceed with studying the causes of RDS in order to reduce the number of unknown ones.

Conclusion

The incidence of RDS in newborns born after week 32 of gestation in the two study periods did not significantly change. What did change are the causes. The leading

cause of RDS was sepsis, the influence of which diminished due to better prenatal care. One of the newly detected causes of RDS was thrombophilia (13% in 2010). Its detection was a consequence of the introduction of thrombophilia testing in pregnant women after the year 2006. The number of known causes of RDS went up in 2010 while the proportion of the unknown causes declined in 2010 with respect to their proportion in 2006. This change in the incidence is not statistically significant ($p>0.05$). In both observation periods, there were more male newborns among infants diagnosed with RDS, though the frequency of the appearance of RDS among male children has decreased over the years whereas this frequency rose among female babies.

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RESPIRATORNI DISTRES SINDROM U NOVOROĐENČADI STARIJE OD 32 GESTACIJSKA TJEDNA

SAŽETAK

Iako su poznati uzroci koji dovode do respiratornog distres sindroma (RDS-a), studijom smo željeli istražiti da li su se isti tijekom dva jednogodišnja razdoblja, 2006. i 2010. godine promijenili. Retrospektivnom studijom su obrađeni podaci 60 novorođenčadi starije od 32 tjedna kojima je dijagnosticiran RDS u Kliničkom bolničkom centru Osijek u Odjelu novorođenačke intenzivne terapije. U radu je ispitana učestalost RDS-a u novorođenčadi starije od 32 tjedna, razlika u pojavnosti RDS-a tijekom dva jednogodišnja razdoblja s odmakom od četiri godine (2006. i 2010.), tražili su se najčešći uzroci RDS-a kod novorođenčadi starije od 32 tjedna te postoji li promjena u istima tijekom promatranog razdoblja. Nađeno je povećanje učestalosti RDS-a u 2010. godini, ali ono nije bilo statistički značajno. Najčešći uzrok RDS-a je u obje godine bila sepsa čiji se udio smanjio u 2010, dok se udio asfiksije i komplikacija u trudnoći povećao ali ne značajno. Novi potencijalni uzrok u 2010. je majčina trombofilija. Smanjio se udio nepoznatog uzroka RDS-a, iako ne statistički značajno. Rezultati ovog istraživanja pokazuju da je došlo do promjene u uzrocima RDS-a tijekom promatranog razdoblja, i da bi daljnjim istraživanjima trebalo pratiti majčinu trombofiliju kao i druge komplikacije u trudnoći i porodu. Tako će se udio novorođenčadi s nepoznatim uzrokom RDS-a zasigurno i dalje smanjivati.