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The influence of prenatal steroid therapy on the occurrence of respiratory disorders and the use of respiratory support in prematurely born infants

Katarzyna Szymoniak[1, A] ✉, Dominika Stasik[2, B], Dorota Ćwiek[1, C], Małgorzata Zimny[1, D], Regina Powirska-Swęd[1], Krystyna Czechowska[1, E]

[1] Pomeranian Medical University in Szczecin, Department of Obstetrics and Pathology of Pregnancy, Żołnierska 48, 71-210 Szczecin, Poland
[2] Independent Public Specialist Healthcare Center "Zdroje", Neonatal, Pathology and Intensive Care Unit, Mączna 4, 70-780 Szczecin, Poland

[A] ORCID: 0000-0003-3941-7340; [B] ORCID: 0000-0003-1080-9316; [C] ORCID: 0000-0002-4908-9056; [D] ORCID: 0000-0003-1695-6966; [E] ORCID: 0000-0003-4404-2846

✉ katarzyna.szymoniak@pum.edu.pl

ABSTRACT

Introduction: Neonatology is a constantly developing branch of medicine. As it has developed, there has been a reduction in mortality rates among prematurely born infants. The main problem faced by premature infants is respiratory disorders. The frequency of neonatal respiratory failure is inversely proportional to the gestational age and the maturity of the gas exchange system.

The aim of this study was to evaluate the effect of steroid therapy in pregnant women on the occurrence of respiratory distress and the need for respiratory support in premature neonates.

Materials and methods: The study covered 100 premature infants born in the Neonatal Intensive Care Unit of Zdroje Specialist Independent Public Health Care Centre in Szczecin. The newborns were divided into research groups, which consisted of newborns with prenatal steroid therapy, and a control group, which consisted of newborns without steroid therapy. The study was retrospective and was carried out based on the analysis of medical records.

Results: Breathing disorders were more frequent in newborns who had received steroid therapy before birth than in children without steroid therapy. Respiratory failure occurred in children who had received both 1 or 2 doses of prenatal steroid therapy. A similar percentage of children, with and without the use of steroid therapy, required mechanical ventilation. Continuous positive airway pressure was applied both in children who had received steroids during pregnancy and those who had not. However, newborns who had received steroids during pregnancy required respiratory support for a shorter time.

Conclusions: 1. Prenatal steroid therapy does not reduce respiratory disorders in prematurely born children. 2. Respiratory support is required more often by newborns without steroid therapy during pregnancy.

Keywords: prenatal steroid therapy; premature infant; respiratory disorders.

INTRODUCTION

Neonatology is a constantly evolving branch of medicine. As it has developed, the mortality rate among premature newborns has decreased. The increase in survival rates mainly concerns extremely premature newborns born before the 28th week of gestation. The main problem faced by premature babies is respiratory distress. The occurrence of neonatal respiratory distress is inversely proportional to the gestational age and the maturity of the system involved in gas exchange. One of the prophylactic methods is prenatal steroid therapy in pregnant women at risk of preterm delivery. The aim of this treatment is to reduce the risk of respiratory disorders in newborns.

The aim of this study was to evaluate the effect of steroid therapy in pregnant women on the occurrence of respiratory distress and the need for respiratory support in premature neonates.

MATERIALS AND METHODS

The study comprised 100 premature neonates who were patients of the Neonatal Intensive Care Unit in the Independent Public Specialist Healthcare Centre Zdroje in Szczecin. The newborns were divided into a study group and a control group. The study group consisted of newborns who received prenatal steroid therapy. The criterion for inclusion in the study was babies born after the 22nd week of gestation. The control group consisted of newborns without steroid therapy. The study group comprised 50.0% of the subjects and the same number of patients were in the control group. The study was retrospective and based on the analysis of medical records of the neonates, from which the following data were obtained: prenatal steroid therapy (time, number of doses, and week of gestation), the birth status of the neonate (Apgar scale, occurrence of respiratory insufficiency, respiratory distress syndrome, and bronchopulmonary dysplasia – BPD), respiratory support (continuous positive airway pressure – CPAP, mechanical ventilation), surfactant administration (number of doses), time of hospitalization. The study did not require the approval of the Bioethics Committee. The study was based on records 2017–2019. Statistical analysis was performed using the SPSS 23 statistical package and Excel. A significance level of $p = 0.05$ was adopted, indicating the presence of statistically significant correlations or differences.

RESULTS

The study group consisted of 100 premature newborns. In the study group, steroid therapy was administered before the 30th week of gestation in 52.0% of the examined children, whereas in 48.0% steroid therapy was administered after the 30th week of gestation. In the study group, 72.0% of the examined children received 2 doses of steroid therapy, while 28.0% received only 1 dose. Out of 100 newborns included in the study, 45.0% had a gestation period of 32–37 weeks and 41.0% had a gestation period of 28–32 weeks. The study has shown that 78.0% of the studied neonates had respiratory distress syndrome, 71.0% had respiratory failure and 85.0% had BPD. Continuous positive airway pressure was used on 90.0% of the neonates, while mechanical ventilation was only used in 35.0% of the children. This is shown in Table 1.

TABLE 1. Characteristics of the study group

Parameter		Total n (%)
Prenatal steroid therapy	study group	50 (50.0)
	control group	50 (50.0)
	total	100 (100.0)
Week of pregnancy when steroid therapy was administered	before 30 weeks	26 (52.0)
	after 30 weeks	24 (48.0)
Doses of steroid therapy	1 dose	14 (28.0)
	2 doses	36 (72.0)
Duration of pregnancy	22–28 weeks	14 (14.0)
	28–32 weeks	41 (41.0)
	32–37 weeks	45 (45.0)
Respiratory distress syndrome	yes	78 (78.0)
	no	22 (22.0)
Respiratory failure	yes	71 (71.0)
	no	29 (29.0)
Bronchopulmonary dysplasia	yes	15 (15.0)
	no	85 (85.0)
Respiratory support – CPAP	yes	90 (90.05)
	no	10 (10.0)
Respiratory support – mechanical ventilation	yes	35 (35.0)
	no	65 (65.0)

CPAP – continuous positive airway pressure

Respiratory distress syndrome was more frequent in newborns who had received steroid therapy before birth (86.0%) than in children without steroid therapy (72.0%). The analysis of the correlation between the time of administering prenatal steroid therapy and the occurrence of respiratory distress syndrome showed that significantly more often respiratory distress syndrome did not affect neonates who had received steroid therapy after the 30th week of gestation (85.7%). Statistical significance was at p = 0.039. This is shown in Table 2.

Respiratory distress syndrome occurred in neonates regardless of the number of doses of steroid therapy (30.2%; 69.8%). However, it was less likely in children who had received 2 doses of steroids (85.7%). This was not statistically significant (p = 0.357). This is shown in Table 3.

TABLE 3. Analysis of the correlation between the number of doses of steroid therapy and the occurrence of respiratory distress syndrome

Respiratory distress syndrome		1	2	Total	p
Yes	n (%)	13 (30.2)	30 (69.8)	43 (100.0)	0.357
No	n (%)	1 (14.3)	6 (85.7)	7 (100.0)	
Total	n (%)	14 (28.0)	36 (72.0)	50 (100.0)	

Similar results were obtained for respiratory failure. Both children who had received 1 dose of steroid therapy and children who had received 2 doses experienced respiratory failure (27.0%; 73.0%). However, it was less common in children who had received 2 doses of steroid therapy (66.7%). Interestingly, respiratory failure occurred at similar rates in both infants without prenatal steroid therapy (68.0%) and with steroid therapy (76.0%). This is shown in Table 4.

The analysis of the material concerning the use of steroid therapy during pregnancy and the need for respiratory support in preterm infants showed that a similar percentage of children without (36.0%) and with (32.0%) prenatal steroid therapy required mechanical ventilation. Similar results were obtained for respiratory support in the form of CPAP. Both children who had received steroids during pregnancy (88.0%) and those who had not (92.0%) received artificial respiratory support. However, a small proportion of newborns after prenatal steroid therapy required this support less frequently. This is shown in Table 5.

The analysis of the correlation between the duration of pregnancy and the frequency of using respiratory support in newborns showed that mechanical ventilation was used significantly more often in neonates born between the 28th and 32nd week of gestation (42.9%) and least often in neonates born between the 22nd and 28th week of gestation (25.7%). Statistical significance was at p = 0.023. This is shown in Table 6.

However, respiratory support in the form of CPAP was required by all premature newborns in a similar proportion, regardless of the week of gestation. Infants born between the 32nd and 37th week of gestation needed CPAP least frequently (50.0%). This was not statistically significant (p = 0.904) and it is presented in Table 7.

TABLE 2. Analysis of the correlation between the time of administering steroid therapy and the occurrence of respiratory distress syndrome

Respiratory distress syndrome			Week of pregnancy when steroid therapy was administered			p
			before 30 weeks n (%)	after 30 weeks n (%)	total n (%)	
Study group	yes	43 (86.0)	25 (58.1)	18 (41.9)	43 (100.0)	0.039
	no	7 (14.0)	1 (14.3)	6 (85.7)	7 (100.0)	
Control group	yes	36 (72.0)	Fisher's exact test = 0.045; df = 1; Cramer's V = 0.305; p = 0.031			
	no	14 (28.0)				

TABLE 4. Analysis of the correlation between the number of prenatal steroid therapy doses and the occurrence of respiratory failure

	Respiratory failure			Number of steroid therapy doses			
				1	2	total	p
Study group	yes	n (%)	38 (76.0)	10 (27.0)	27 (73.0)	37 (100.0)	0.468
	no	n (%)	12 (24.0)	4 (33.3)	8 (66.7)	12 (100.0)	
Control group	yes	n (%)	34 (68.0)	Fisher's exact test = 0.721; df = 1			
	no	n (%)	16 (32.0)				

TABLE 5. Type of respiratory support used in newborns

Type of respiratory support	Study group		Control group		Total
	yes n (%)	no n (%)	yes n (%)	no n (%)	n (%)
Mechanical ventilation	16 (32.0)	34 (68.0)	18 (36.0)	32 (64.0)	100 (100.0)
CPAP	44 (88.0)	6 (12.0)	46 (92.0)	4 (8.0)	100 (100.0)

CPAP – continuous positive airway pressure

TABLE 6. Analysis of the correlation between the duration of pregnancy and the use of mechanical ventilation in newborns

Mechanical ventilation		Duration of pregnancy				
		22–28 weeks	28–32 weeks	32–37 weeks	total	p
Yes	n (%)	9 (25.7)	15 (42.9)	11 (31.4)	35 (100.0)	0.023
No	n (%)	5 (7.7)	26 (40.0)	34 (52.3)	65 (100.0)	
Total	n (%)	14 (14.0)	41 (41.0)	45 (45.0)	100 (100.0)	

χ^2 = 7.53; df = 2; Cramer's V = 0.274

TABLE 7. Analysis of the correlation between the duration of pregnancy and the use of respiratory support – CPAP

CPAP		Duration of pregnancy				
		22–28 weeks	28–32 weeks	32–37 weeks	total	p
Yes	n (%)	13 (14.4)	37 (41.1)	40 (44.4)	90 (100.0)	0.904
No	n (%)	1 (10.0)	4 (40.0)	5 (50.0)	10 (100.0)	
Total	n (%)	14 (14.0)	41 (41.0)	45 (45.0)	100 (100.0)	

χ^2 = 0.191; df = 2; CPAP – continuous positive airway pressure

It is important to note that there are no statistically significant differences between the duration of respiratory support in children and the use of prenatal steroid therapy (p = 0.706). However, neonates who had received steroids during pregnancy required respiratory support for a shorter time. The median time where respiratory support was needed in this group was less than 10 days (9.54). This is shown in Table 8.

TABLE 8. Analysis of the differences between the duration of respiratory support and the use of steroid therapy

Group		n	M	SD	U	p
Duration of respiratory support	study	50	9.54	11.05	1195.50	0.706
	control	50	11.22	14.20		

The correlation between the frequency of surfactant use in preterm infants during their stay in the Intensive Care Unit and the use of prenatal steroid therapy was also analysed. In the study group, surfactant was used less frequently (34.0%; 10.0%) than in the control group (46.0%; 20.0%). This suggests that children who had received prenatal steroid therapy required surfactant after birth less frequently. Statistical significance was at p = 0.072. This is shown in Table 9.

TABLE 9. Analysis of the correlation between the number of surfactant doses in newborns and the use of steroid therapy

Group		Number of surfactant doses				
		none	1	2	total	p
Study	n (%)	28 (56.0)	17 (34.0)	5 (10.0)	50 (100.0)	0.072
Control	n (%)	17 (34.0)	23 (46.0)	10 (20.0)	50 (100.0)	
Total	n (%)	45 (45.0)	40 (40.0)	15 (15.0)		

χ^2 = 5.26; df = 2

An analysis of the material in terms of the correlation between the number of doses of steroid therapy and the duration of neonatal hospitalization showed that when steroid therapy was not administered during pregnancy, neonatal hospitalization lasted over 2 months more often (30%), whereas only 14.3% of neonates with 1 dose of steroids and 27.8% with 2 doses of steroid therapy were hospitalized for over 2 months. However, this was not statistically significant (p = 0.072) and is presented in Table 10.

TABLE 10. Analysis of the correlation between the number of doses of steroid therapy and the duration of neonatal hospitalization

Number of steroid therapy doses		Duration of hospitalization				
		<1 month	1–2 months	>2 months	total	p
None	n (%)	25 (50.0)	10 (20.0)	15 (30.0)	50 (100.0)	0.072
1	n (%)	4 (28.6)	8 (57.1)	2 (14.3)	14 (100.0)	
2	n (%)	12 (33.3)	14 (38.9)	10 (27.8)	36 (100.0)	
Total	n (%)	41 (41.0)	32 (32.0)	27 (27.0)	100 (100.0)	

χ^2 = 8.58; df = 2

An important aspect of the study was an analysis of the correlation between the use of steroid therapy during pregnancy and the occurrence of BPD in newborns. As many as 50% of neonates without steroid therapy suffered from BPD. However, in children after 1 dose of steroids, this percentage was 14.3% and after 2 doses it was 35.7%. This was not statistically significant (p = 0.999) and is presented in Table 11.

TABLE 11. Analysis of the correlation between the use of steroid therapy and the occurrence of bronchopulmonary dysplasia

Bronchopulmonary dysplasia		Number of steroid therapy doses				
		none	1	2	total	p
Yes	n (%)	7 (50.0)	2 (14.3)	5 (35.7)	14 (100.0)	
No	n (%)	43 (50.6)	12 (14.1)	30 (35.3)	85 (100.0)	0.999
Total	n (%)	50 (50.5)	14 (14.1)	35 (35.4)	99 (100.0)	

χ^2 = 0.002; df = 2

The Apgar scale is the 1st examination in the life of a newborn and is used to assess 5 basic vital functions. Analysis of the correlation between the time from prenatal steroid administration to delivery and the neonatal Apgar score showed no statistically significant differences (p = 0.391). The majority of newborns who had received steroids more than 48 h before delivery and those who had received steroids up to 24 h before delivery received medium Apgar scores (51.5%; 70.6%). This is shown in Table 12.

TABLE 12. Analysis of the correlation between the time from steroid administration to delivery and the neonatal Apgar score

Time from steroid administration to delivery		Apgar scale				
		low score	medium score	high score	total	p
<24 hours	n (%)	1 (5.9)	12 (70.6)	4 (23.5)	17 (100.0)	0.391
>48 hours	n (%)	2 (6.1)	17 (51.5)	14 (42.4)	33 (100.0)	
Total	n (%)	3 (6.0)	29 (58.0)	18 (36.0)	50 (100.0)	

χ^2 = 1.88; df = 2

DISCUSSION

Steroids are the most effective drug administered to pregnant women which contribute to accelerated lung maturation [1]. In Poland, no detailed data regarding the actual frequency of glucocorticosteroid use in pregnant women are currently collected, although this therapy is a simple and accessible way of preventing many complications of preterm labour.

This study showed that the occurrence of respiratory distress syndrome was dependent on the time of steroid therapy. The incidence was lower in the group of newborns born after the 30th week of pregnancy. This may be due to the maturity of the respiratory structures in the foetus. Respiratory distress was statistically more frequent in the group of neonates born before 30 weeks of gestation, which is related to the degree of lung development. Mori et al. demonstrated that in neonates born before the 26th or after the 33rd week of gestation, antenatal corticosteroid administration may have limited beneficial effects [2]. Other studies by Liu et al. and Kim et al. confirm the effectiveness of prenatal steroid therapy by demonstrating an increased survival rate in extremely premature neonates born before the 33rd week of gestation [3, 4]. It would be worth extending research in this direction by collecting data on neonates born at particular weeks of gestation, not limited to time ranges, which could provide further clues for planning preventive measures in the management of preterm labour and care of children born prematurely.

In this study, steroid therapy was based on intramuscular administration of 2 doses of betamethasone to pregnant women 24 h apart, which constitutes a full prophylactic course. When analysing the correlation between the number of steroid therapy doses and the incidence of respiratory distress, a better effect was found after a full course of steroid therapy. This study shows that the use of 1 or 2 doses has a similar effect in reducing the incidence of respiratory distress syndrome and respiratory failure in premature newborns. In their study, Romejko-Wolniewicz et al. present similar results indicating limited benefits of incomplete courses of steroid therapy in reducing the incidence of respiratory distress [5]. This may be due to a reduced dose of corticosteroids and shorter foetal exposure time. In contrast, an analysis by Wong et al. shows that neonatal mortality rates are higher in extremely premature infants who do not receive antenatal steroid therapy. A partial course of steroid treatment reduces the incidence of intraventricular haemorrhage and mortality among infants born between the 24th and 35th week of gestation but has no significant effect on the incidence of respiratory distress. Infants not receiving therapy are more likely to develop necrotising enterocolitis (NEC) and have 3rd- and 4th-degree intraventricular haemorrhages. The authors also focus on comparing the effects of steroid therapy after a single full course and repeating it after 7 days [6]. In their study, Asztalos et al. show no decrease in mortality and respiratory distress after repeated administration of a full course of corticosteroids after the 32nd week of pregnancy [7]. However, Vogel et al. show increased neonatal mortality after multiple courses of corticosteroids [8].

Most preterm infants usually require respiratory support after birth. Among the neonates included in the study, 42.9% of them, born between the 28th and 32nd week of gestation, required intubation and mechanical ventilation. Neonates born after the 32nd week of pregnancy constituted 31.4% of neonates requiring intubation, whereas extremely premature neonates born before the 28th week of gestation constituted 25.7% of the whole group. The analysis of the results suggests that this may be due to the differences in the number of newborns included in the study assigned to the respective gestational age groups. On the other hand, currently, efforts are being made in neonatology

to provide respiratory support just after birth with less invasive methods, thus avoiding the need for intubation.

This research compared the frequency of CPAP use in different age groups of newborns and showed the following trend: the more mature the newborn, the more often respiratory support began with CPAP. This is related to the child's birth status and also to the maturity of the body. Newborns born after the 32nd week (representing 44.4% of the group) initiate their own respiratory activity and only require respiratory support, which is provided by the CPAP. The analysis shows that documenting the method of respiratory support that is 1st applied in a premature newborn would be important in considering the impact of steroid therapy on respiratory distress.

The study compared the duration of respiratory support in newborns in 2 groups: those born from pregnancies with a prenatal course of steroid therapy and those born from pregnancies without prophylactic steroid therapy. No statistically significant differences were observed between the duration of respiratory support and the use of steroid therapy. However, Pilewska-Kozak indicates that prenatal steroid therapy affects the duration of treatment of neonates with respiratory failure by reducing the incidence of severe forms of respiratory distress, which may shorten the duration of using respiratory ventilation and reduce its parameters in premature infants [9]. However, in the available literature, there are no detailed studies analysing the relationship between prenatal steroid therapy and the type and duration of ventilatory support in preterm infants. Studying the correlation between these elements could provide key insights into the planning of care for the pregnant woman and the prevention of risks associated with preterm birth. The results of this study can be compared with those of Liu et al., who shows that infants born between the 25th and 34th week of gestation and exposed to antenatal corticosteroids have a lower rate of mechanical ventilation at birth, but this effect is not statistically significant for infants before the 25th week of pregnancy [3].

The analysis of the correlation between antenatal steroid therapy and surfactant administration in the Neonatal Intensive Care Unit showed that in the study group, surfactant was used in newborns less frequently (56.0%) than in the control group (34.0%). The frequency of 1 dose surfactant administration decreased from 43% to 34%, while the frequency of 2 dose administration decreased from 20% to 10%. This demonstrates a positive effect of corticosteroids in pregnant women at risk of preterm delivery on minimising the need for surfactant administration in premature neonates. A study by Rojas-Reyes et al. shows that prophylactic surfactant use after previous antenatal steroid therapy leads to better outcomes in babies at risk of respiratory distress compared to implementing treatment for developing respiratory failure [10]. Surfactant is essential for normal lung function in neonates. Its administration finds application in both the prevention and treatment of respiratory distress.

This study showed that the hospitalisation of infants who had not received prenatal steroid therapy lasted up to 1 month in 50% of cases. In the case of a 1 dose administration, hospitalisation lasting up to a month concerned 28.6% of the children, while in the case of a 2 dose administration, this figure rose to 33.3% of the cases. Therefore, it can be deduced that shorter hospitalisation times of neonates not receiving steroid therapy is due to their maturity and good general health. In the case of more premature neonates, hospitalization is prolonged not only due to respiratory disorders but also due to extremely low body weight. A longer stay in the Neonatal Intensive Care Unit is mainly determined by the time needed to develop respiratory function and adequate body weight. Among the neonates who stayed in the hospital for more than 2 months, 14.3% of the group received 1 dose of steroid therapy and 27.8% of the group received 2 doses. This confirms the hypothesis that steroid therapy reduces the length of hospitalisation of more mature neonates.

This study showed no statistically significant correlation between the number of steroid therapy doses and the occurrence of BPD in children. This is supported by similar studies on this topic. Gien and Kinsella demonstrated that antenatal corticosteroid use in mothers at risk of preterm delivery unambiguously reduced neonatal mortality and the incidence of respiratory distress syndrome, but despite combining this method with surfactant use in newborns immediately after birth, it does not reduce the incidence of BPD [11].

The correlation between the condition of the newborn immediately after birth and the time since the completion of the steroid therapy course was also investigated. No statistically significant correlation was found in this regard. According to Chawla et al., it is likely that the therapy does not affect the well-being of the neonate and the need for resuscitation immediately after birth, but only the subsequent adaptation to ectopic life [12]. The aforementioned timing may be important given the occurrence of respiratory distress, the main focus of the topic under consideration. According to Jobe and Goldenberg, in neonates born before the 32nd week of gestation, the interval between exposure to antenatal corticosteroids and delivery does not affect the Apgar score after birth [13]. However, the authors indicate that a prenatal course may be associated with a reduced incidence of respiratory distress only if the time between the end of the course and the delivery is between 2–7 days.

CONCLUSIONS

1. Prenatal steroid therapy does not reduce respiratory distress in preterm infants.
2. Not all preterm infants require respiratory support, but infants without steroid therapy during pregnancy require it more often.

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