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Georgios Konstantinidis^{1,2}, Vesna Pavlović^{1,2}, Aleksandra Stojadinović^{1,2}, Katarina Katić^{2,†}

**Characteristics and morbidity of prematurely born newborns conceived
with assisted reproductive technologies**

Карактеристике и морбидитет превремено рођене новорођенчади зачете
вантелесном оплодњом

¹University of Novi Sad, Faculty of Medicine, Novi Sad, Serbia;

²Institute of Health Care of Children and Adolescents of Vojvodina, Novi Sad, Serbia

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†Correspondence to:

Katarina KATIĆ

Braće Jovandića 7, 21000 Novi Sad, Serbia

E-mail: ranko.zdravkovic@ikvbn.ns.ac.rs

Characteristics and morbidity of prematurely born newborns conceived with assisted reproductive technologies

Карактеристике и морбидитет превремено рођене новорођенчади зачете вантелесном оплодњом

SUMMARY

Introduction/Objective The proportion of live-born infants conceived with assisted reproductive technologies (ART) in some European countries reaches 6% and in Serbia over 1%.

The aim of this study was to analyze characteristics and morbidity of prematurely born newborns conceived with ART.

Methods The study included 154 prematurely born newborns from pregnancies conceived with ART and 154 prematurely born newborns conceived naturally hospitalized at the Institute of Health Care of Children and Adolescents of Vojvodina. Participants from both groups were matched according to gestational age and date of birth.

Results Statistically significantly more newborns with very low birth weight have been in group of newborns conceived by ART in comparison to newborns conceived naturally (χ^2 test, $p = 0.0002$). Morbidity of newborns conceived with ART is not higher in comparison to newborns of the same gestational age conceived naturally. Bronchopulmonary dysplasia, occurred more frequently in children from ART (χ^2 test, $p = 0.006$) and retinopathy of prematurity, occurred more frequently in children spontaneously conceived. (χ^2 test, $p = 0.047$). There was no difference in the frequency of birth defects, genetic syndromes and inborn errors of metabolism between two groups.

Conclusion Lower birth weight and intrauterine growth restriction are potential risk factors for worse postnatal outcome in newborns from pregnancies conceived with ART.

Keywords: assisted reproductive technologies; prematurely born newborns; morbidity

САЖЕТАК

Увод/Циљ Удео живорођене новорођенчади зачете неком од метода вантелесне оплодње (асистиране репродуктивне технологије – АРТ) у сталном је порасту. У неким европским земљама досеже и 6% . У Србији је он нешто више од 1%. Циљ рада је био да се анализирају карактеристике и морбидитет превремено рођене новорођенчади из АРТ.

Метод Студија је обухватила 154 превремено рођена новорођенчета зачета вантелесном оплодњом и 154 превремено рођена новорођенчета зачета природним путем, који су били хоспитализована у Института за здравствену заштиту деце и омладине Војводине. Испитаници из обе групе су уједначени према гестациској старости и датуму рођења.

Резултати У нашем истраживању било је статистички значајно више новорођенчади са врло малом порођајном масом у групи новорођенчади из АРТ трудноћа у односу на новорођенчад из спонтано зачетих трудноћа (χ^2 тест, $p = 0,0002$). Стопа морбидитета превремено рођене деце зачете вантелесном оплодњом није већа у односу на превремено рођену децу зачету природним путем. Бронхопулмонална дисплазија (χ^2 тест, $p = 0,006$) се јавља чешће код деце зачете вантелесном оплодњом, а ретинопатија прематуритета (χ^2 тест, $p = 0,047$) се јавља чешће код деце зачете природним путем исте гестациске старости. Није било разлике у учесталости конгениталних аномалија, генетских синдрома и метаболичких поремећаја између група.

Закључак Мала порођајна маса и интраутерине застој раста су потенцијални фактори ризика за лошији постнатални исход код новорођенчади из трудноћа зачетих АРТ.

Кључне речи: асистиране репродуктивне технологије; превремено рођена новорођенчад; морбидитет

INTRODUCTION

According to the European Society of Human Reproduction and Embryology, from 1997 to 2014 there have been a reported 1,478,452 newborns conceived with assisted reproductive technologies (ART) [1] The number of prematurely born infants is significantly

higher with assisted conception than the number of infants born from natural conception. To solve this health and, ultimately, the social problem in Serbia, in 2006 the Republic Health Insurance Fund started financing the program of ART conceptions.

Research and identification of short and long-term effects of ART are very challenging tasks. First and foremost, the reason for this is great heterogeneity in collecting, classifying, analyzing and interpreting the enormous amount of information gathered so far in various studies. Individual approach to infertility treatment, fast improvement and constant changes in the methodology of ART together with previously mentioned problems of data collection and analysis, significantly impede the possibility to accurately comprehend all possible risks and consequences of artificial conception. Despite numerous studies, scientific publications and accumulated evidence there are still a lot of perplexity in reference to the questions: Whether the (artificially) assisted reproduction represents greater risk for inadequate embryo development, poorer perinatal outcome and what the long term consequences for the children are, as well as whether the risks are equal for single and multiple pregnancies conceived by ART [2–5].

Children born from pregnancies with medically assisted conception have higher risks of intrauterine growth retardation (IUGR), low birth weight (LBW), preterm delivery, and different congenital malformations all of which could suggest the possibility of disrupted or suboptimal intrauterine growth.

A great deal of the above-mentioned problems has been explained by the fact that majority of pregnancies achieved by some of the medically assisted reproduction techniques were dominantly multiple pregnancies with additional risks of mother's age and morbidity, therefore carrying higher risks of suboptimal fetal growth [6]. Nevertheless, this claim is only partially true.

Etiologic factors and pathophysiological mechanisms that influence fetal growth and development can be of intrinsic and extrinsic nature. Intrinsic factors refer to characteristics of the fetus itself and include chromosomal abnormalities, chronic fetal infection, congenital malformations, and genetic variations. Extrinsic factors can be divided into maternal and uteroplacental. Among maternal factors, there are mother's periconceptional body weight, height (and age, and periconceptional nutritive status. Maternal pregnancy factors that define fetal growth and development are the existence of the cardiovascular disease, development of

pregnancy hypertension syndrome, gestational diabetes, renal diseases, decreased oxygenation, inadequate nutrition during pregnancy, smoking, taking alcohol and medicines and other chemicals [3, 7]. Uteroplacental factors that negatively affect fetal growth and development are placental insufficiency, disorders of placentation and occurrence of multiple pregnancies.

Regardless of causes, the infant born with ART is the infant with potentially poorer perinatal outcome mainly because of a higher percentage of multiple pregnancies, higher frequency of preterm deliveries and unwanted outcomes of the ART [8]. In spite of this, In Serbia and in the other regions on the former territory of Yugoslavia, the papers on in vitro fertilization (IVF) on perinatal and neonatal statistics are very scarce.

The aim of this study was to establish the structure of morbidity of preterm infants conceived with ART (in single and multiple pregnancies) treated at the Institute for Health Care of Children and Youth Of Vojvodina and to identify perinatal factors that are connected with the occurrence of acute and chronic complications and diseases of prematurely born newborns conceived with ART.

METHODS

The study included preterm infants hospitalized at the Department for Neonatology and Intensive and Semi-Intensive Care and Therapy at the Institute for Healthcare of Children and Youth of Vojvodina in Novi Sad. The retrospective study included newborn babies born between 01/01/2011. and 31/12/2012. and treated at the Department. Data on patients included in the retrospective part of the study were collected from medical records.

From this cohort, two groups were formed: the examine group (Group 1) included all prematurely born babies conceived with ART and hospitalized and treated at the Institute during the given period of time. The control group (Group 2) included all preterm born babies conceived naturally. Babies in the control group were chosen from the cohort so that their number would correspond to the number of babies in the first examine group. Participants from both groups were matched according to gestational age (GA) and date of birth. GA of the babies from the control group does not differ more than ± 4 days than that of the babies

from the experimental group. Date of birth of the babies from the control group does not differ more than ± 3 months than one of the babies from the experimental group.

A detailed algorithm for the selection of respondents included in the study is given in Figure 1.

At the time of the inclusion in the study the following data in reference to the baby were considered: intrauterine infection, IUGR, delivery method, Apgar score (AS), anthropometric parameters (body weight, body length, head circumference) at birth, duration of child's initial hospitalization, duration of invasive and/or non-invasive respiratory support and oxygen therapy, hospital discharge diagnosis (the presence of severe consequences of prematurity, which include intracranial hemorrhage of 3rd and 4th degree (defined in International Classification of Disease-Tenth Revision (ICD-10) under code P 52.2), cystic periventricular leukomalacia, retinopathy of prematurity (ROP), bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC), sepsis and/or meningitis (microbiologically or clinically diagnosed), presence of congenital anomalies or genetic syndromes and diseases (defined in ICD-10 under codes Q00 to Q99) as well as the presence of inborn errors of metabolism (defined in ICD-10 under codes E00 to E90). The subjects' written consent was obtained, according to the Declaration of Helsinki, the study has been approved by competent ethics committee of the Institute of Health Care of Youth and Adolescents of Vojvodina.

RESULTS

The examined group (group 1) consisted of 154 prematurely born newborn babies conceived with ART from 87 mothers. Out of the total, there were 33 newborns from singleton pregnancies while 121 were born from multiple pregnancies (39 from trigeminal and 82 from twin pregnancies).

The control group (group 2) was formed according to previously described methodology from prematurely born infants of approximately the same GA from naturally conceived pregnancies. This group comprised 154 preterm born newborn infants from 138 mothers. There were 122 newborns from singleton pregnancies while 32 newborns were from twin pregnancies (16 twin pregnancies all together).

The main characteristics of newborns from Group 1 and Group 2 are given in Table 1.

There has been no statistically significant difference in infants of group 1 and group 2 according to GA and gender (Student's t-test, $p = 0.152$).

There has been a statistically significant difference in birth weight (BW) of newborns from group 1 and group 2. Newborns from group 1 had on average lower body weight on birth (Student's t-test, $p = 0.049$). The average difference in BW between newborns in group 1 and group 2 was 59.427g.

The proportion of newborns with a BW under 1500g (very low BW), birth weight from 1500g to 2499g (low BW) and birth weight ≥ 2500 g, in both groups are shown in Figure 2.

Statistically, significantly more newborns with very low BW have been in group 1 in comparison to group 2 (χ^2 test, $p = 0.0001$). The number of newborns with BW ≥ 2500 g has been the same in both groups (χ^2 test, $p = 0.702$). There has been no statistically significant difference in body length at birth and head circumference in newborns of both groups (Student's t-test, $p = 0.992$, $p = 0.13$).

Newborns from group 1 have had a significantly higher AS in the 1st minute in comparison to newborns from group 2 (Student's t-test, $p = 0.034$). The values of AS in the 5th minute have had no statistically significant difference between the two groups (Student's t-test, $p = 0.054$).

There has been no statistically significant difference in frequency of symmetrical and asymmetrical IUGR between the two groups of participants (Fisher's exact test of probability, $p = 0.394$).

The average duration of hospitalization, the average length of respiratory support and oxygen therapy and morbidity structure (diagnosis at hospital discharge) of children from both groups are given in Table 2. Only the diagnoses listed in the methodology of work have been recorded.

The average duration of hospitalization has been statistically significantly shorter with newborns of group 1 in comparison to group 2. (Student's t-test, $p = 0.012$). The average duration of usage of mechanical respiratory support has been shorter with newborns of group 1. The difference has been statistically significant. (Student's t-test, $p < 0.01$) (Table 2).

Duration of non-invasive respiratory support and oxygen therapy was on average slightly shorter in newborns of group 1 in comparison to newborns of group 2, but the difference was not statistically significant (Student's t-test, $p = 0.052$, $p = 0.472$).

The frequency of ROP was statistically significantly lower in newborns of Group 1 than Group 2 (χ^2 test, $p = 0.047$). Newborns of Group 1 had a lower relative risk for ROP development (RR = 0.6316; CI 0.399–1.00) in comparison to newborns of Group 2.

The frequency of BPD was statistically significantly higher in newborns of Group 1 (RR = 2.823; CI 1.355–5.879) than in newborns of Group 2.

The incidence of higher-grade intracranial hemorrhage, periventricular leukomalacia, NEC, sepsis/meningitis was similar in both groups (χ^2 test, $p = 0.692$, $p = 0.759$, $p = 0.428$, $p = 0.771$).

There were no participants with diagnosed inborn errors of metabolism in either of the groups in the given period of time.

The overall frequency of congenital anomalies and genetic syndromes (defined under the 10th revision of the International Classification of Disease starting from Q00 to Q99) did not differ significantly between groups (χ^2 test, $p = 0.354$).

The structure of congenital malformations and the distribution of their absolute frequencies according to groups is given in Figure 3.

In most cases, there were simple heart defects that were registered in participants of both groups. In Group 1 there were 16 newborns with registered atrial septal defect, while there were 21 of them in Group 2. The difference was not statistically significant (χ^2 test, $p = 0.381$). Ventricular septal defect (small and medium) was registered in two cases with newborns of Group 2. This difference was not statistically significant. (Fisher's test of exact probability, $p = 0.684$). The other listed/ mentioned congenital anomalies occurred occasionally.

DISCUSSION

According to anthropometric parameters at birth and presence of IUGR, the study results show that prematurely born infants conceived by ART in comparison to prematurely born newborns conceived naturally are statistically significantly different in terms of BW and incidence of IUGR. In the group of newborns who were conceived by ART, there were significantly more newborns with very low BW. The average difference between the body weight of newborns conceived by IVF and those conceived naturally was $-59.472 \pm 426.340\text{g}$. The dominant form of IUGR was asymmetrical intrauterine growth restriction, and it was significantly less frequent in the control group.

Most of the studies carried out so far confirm these results. Lei's et al. results showed that artificial conception increases the risk of LBW [9].

In review article Šljivančanin and Kontić-Vučinić state that different studies' conclusion showed that infants from ART have significantly worse perinatal outcome (LBW, VLBW, SGA) compared with natural conception [10]. This fact has been confirmed in our research too.

In a sample of our participants (Group 1), the value of AS in the 1st minute of life was statistically significantly higher than the value of AS in the control group of prematurely born infants. In studies available for us there were most often reported lower values of AS in the 1st and 5th minute of life of newborns conceived with ART [11, 12, 13]. The difference in the results of our findings can be mostly explained by the fact that pregnancies conceived by ART in Serbia are more frequently and more patiently monitored and therefore, the likelihood of early delivery is a better anticipated and better strategy for premature birth has been developed. On the other hand, premature births in spontaneously conceived pregnancies are usually caused by unexpected events related to the health situation of the fetal mother; they were sudden and "unplanned", which significantly influenced the delivery, immediate prenatal treatment of the pregnant woman and the fetus, and accordingly influenced the "condition" of the child immediately after birth. The most common cause of premature birth in the control group was premature contractions, with no significant previous medical history, and the cesarean section was more often indicated in pregnancies conceived with IVF. The value of AS in the 5th minute did not differ significantly between the groups, but newborns that were spontaneously conceived had a higher AS (increase), which could point to the

possibility that spontaneously conceived infants had a slightly more prompt reaction after initial stabilization and a slightly better capacity to adapt to extrauterine conditions of life.

As indicators of neonatal morbidity, in this study, we observed the total length/duration of hospitalization, the number of days on mechanical respiratory support, the number of days on non-invasive respiratory support, the duration of oxygen therapy and significant diagnosis when discharged from hospital (high intracranial hemorrhage, periventricular leukomalacia, ROP, BPD, NEC, sepsis / meningitis, and congenital malformations, genetic syndromes and inborn errors of metabolism. From all the observed parameters/categories, in this study, statistically significantly different among the groups were shown: length of hospitalization, duration of mechanical respiratory support, and frequency of BPD and ROP. Infants conceived with ART had a shorter time spent on mechanical respiratory support and were earlier discharged from hospital (shorter hospitalization), and from the disease - more often had a diagnosed BPD. Children from the control group were more often diagnosed with ROP.

Taking into consideration controversial discussions among professionals about the connection of IVF procedures and congenital malformations, we emphasize as a significant data, that in our sample of prematurely born newborns, there was no difference in the frequency of birth defects, genetic syndromes and inborn errors of metabolism between newborns conceived naturally and those conceived by ART. This result is most likely the result of well-organized and comprehensive monitoring of ART initiated pregnancies (regular examinations, expert ultrasound, etc.). In contrast with our results Giorgione et al. concluded that fetuses conceived with IVF/ICSI methods are at an increased risk of developing CHD compared with those conceived spontaneously [14].

Generally, the observations mentioned in this study are in agreement with the results of other studies that dealt with immediate and short-term outcomes in prematurely born newborns conceived by ART [3, 15, 16]. Disagreement exists in the results that refer to the frequency of BPD and ROP. In a study conducted by Corchia et al., the results indicate that the assisted conception represents a protective factor in relation to BPD, which is in collision with the findings of our study [17]. Also, unlike our study, Corchia et al.'s study has shown that there is no significant difference in the incidence of ROP between prematurely born newborns conceived with ART and those who were spontaneously conceived. By contrast, another study found an increased incidence of both BPD and ROP in babies who were conceived by IVF [16].

In the light of recent events due to COVID-19 pandemic, the major scientific societies have provided recommendations to suspend IVF treatments in order to support healthcare systems by avoiding putting them under additional risk [18, 19].

Although there is no evidence that the virus causing COVID-19 might have negative effects on IVF outcomes, the possibility of the virus affecting sperm function and egg performance cannot be excluded [18]. Though, the prolonged lockdown of health services providing fertility treatments might be detrimental for society as a whole, and infertility patients in particular [20].

These are new challenges in the field of reproductive medicine, which leads to further research regarding characteristics and morbidity of newborns conceived with assisted reproductive technologies during the COVID-19 pandemic.

CONCLUSION

Morbidity of prematurely born newborns conceived with ART is not higher in comparison to prematurely born newborns of the same gestational age conceived naturally. In the morbidity structure of newborns conceived with ART, the same diseases and complications are present as among prematurely born newborns of the same gestational age conceived naturally. Frequency of some diseases is similar, with the exception of BPD, which occurs more often among prematurely born newborns conceived with ART, and retinopathy of prematurity which occurs more often in prematurely born newborns conceived naturally. Lower BW and IUGR are potential risk factors for worse postnatal outcome in newborns from pregnancies conceived with ART. AS in the 1st minute of prematurely born newborns conceived with ART is higher in comparison to AS of prematurely born newborns conceived naturally.

NOTE

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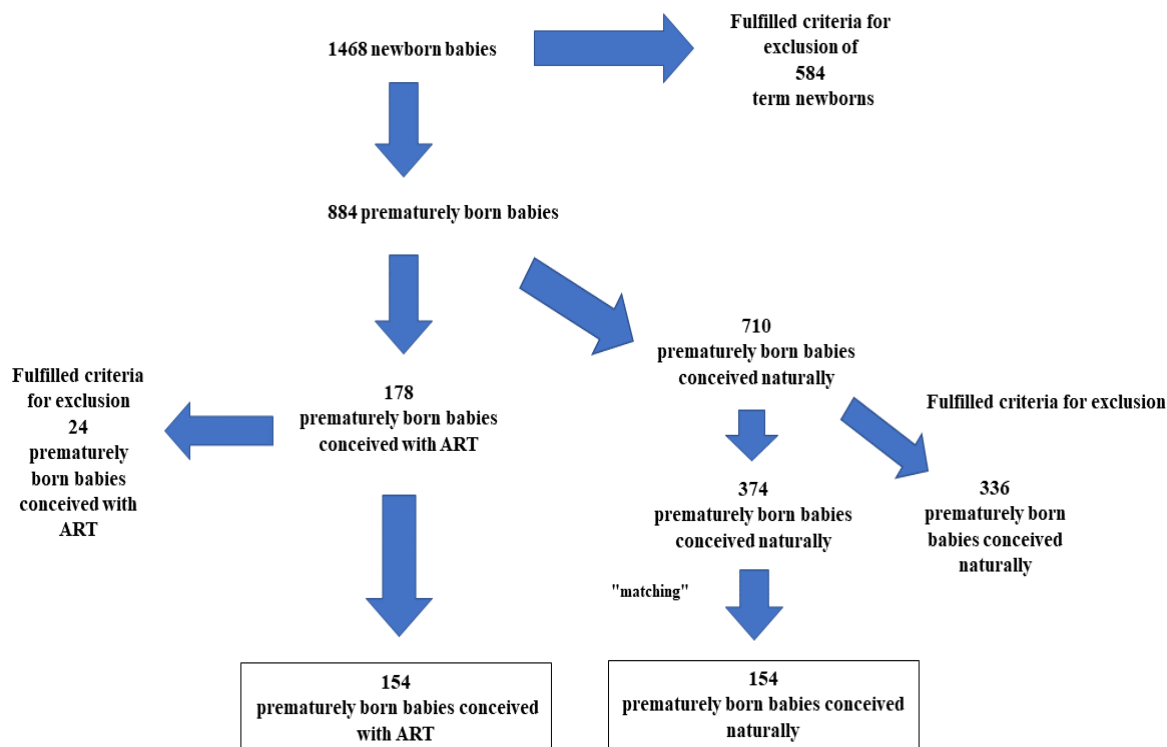


Figure 1. Algorithm for selection of respondents included in the study

Paper

Table 1. Main characteristics of infants according to group

| Characteristic | Group 1 (No 154) | Group 2 (No 154) | p |
|-------------------------|------------------------|----------------------|--------------|
| GA \pm SD (weeks) | 31.829 \pm 2.105 | 31.167 \pm 2.138 | 0.152 |
| Sex (female/male) | 68/86 | 68/86 | / |
| BW \pm SD (g) | 1537.516 \pm 401.594 | 1924.6 \pm 777.843 | 0.049 |
| BL \pm SD (cm) | 41.255 \pm 3.415 | 41.25 \pm 3.536 | 0.992 |
| HC \pm SD (cm) | 29.137 \pm 1.686 | 29.547 \pm 2.309 | 0.130 |
| AS in 1st min. \pm SD | 5.712 \pm 1.750 | 5.1667 \pm 2.133 | 0.034 |
| AS in 5th min. \pm SD | 7.307 \pm 1.210 | 7.012 \pm 0.938 | 0.054 |
| IUGR (%) | 24/154 (15.584) | 10/154 (6.493) | 0.011 |

GA – gestational age; BW – birth weight; BL – birth length; HC – head circumference, AS – Apgar score; IUGR – intrauterine growth restriction; values in bold are statistically significant

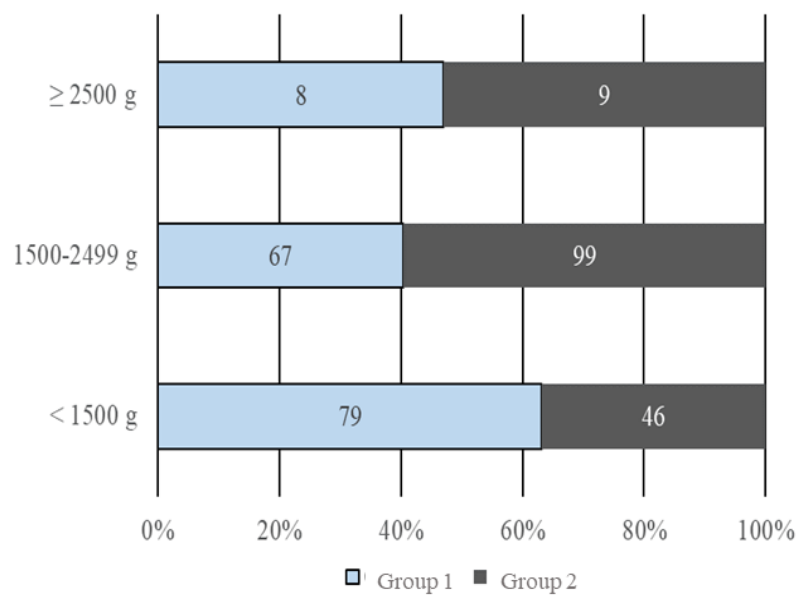


Figure 2. Proportion and absolute frequency of newborns of very low, low, and normal body weight in both groups of newborns

Table 2. The average duration of hospitalization, average length on respiratory support and oxygen therapy, and structure of morbidity at the discharge from hospital

| Parameter | Group 1 (n = 154) | Group 2 (n = 154) | p |
|---|-------------------|-------------------|------------------|
| Length of hospitalization ± SD (days) | 33.294 ± 15.998 | 38.351 ± 14.759 | 0.012 |
| MV (days) | 2.0719 ± 2.779 | 6.447 ± 4.872 | < 0.01 |
| nCPAP (days) | 4.0719 ± 2.117 | 5.512 ± 3.202 | 0.052 |
| Oxygen therapy (days) | 14.046 ± 11.714 | 13.138 ± 4.391 | 0.472 |
| ICH (III i IV degree) | 13/154 | 15/154 | 0.692 |
| PVL | 6/154 | 5/154 | 0.759 |
| ROP | 24/154 | 38/154 | 0.047 |
| BPD | 24/154 | 9/154 | 0.006 |
| NEC | 16/154 | 12/154 | 0.428 |
| Sepsis/meningitis | 30/154 | 28/154 | 0.771 |
| Congenital anomalies and genetic syndromes (ICD-10 codes from Q00 to Q99) | 22/154 | 28/154 | 0.354 |
| Inborn errors of metabolism (ICD-10 codes from E00 to E90) | 0/154 | 0/154 | / |

MV – mechanical ventilatory support; nCPAP – nasal continuous positive airway pressure; ICH – intracranial haemorrhage; PVL – periventricular leukomalacia; ROP – retinopathy of prematurity; BPD – bronchopulmonary dysplasia; NEC – necrotizing enterocolitis; ICD-10 – International Classification of Diseases 10th revision; values in bold are statistically significant

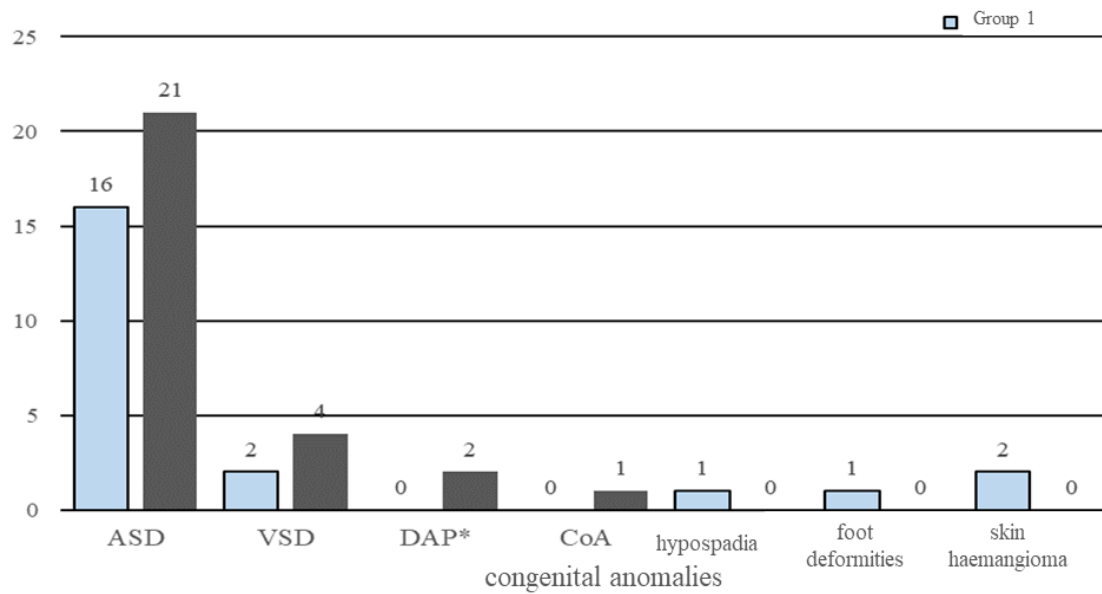


Figure 3. Structure of congenital anomalies and distribution of their absolute frequencies according to groups of participants;

ASD – atrial septal defect; VSD – ventricular septal defect; DAP – persistent arterial duct after the age of six months; CoA – coarctation of the aorta