

ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

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

Georgios Konstantinidis^{1,2}, Vesna Pavlović^{1,2}, Aleksandra Stojadinović^{1,2}, Katarina Katić²¹University of Novi Sad, Faculty of Medicine, Novi Sad, Serbia;²Institute of Health Care of Children and Adolescents of Vojvodina, Novi Sad, Serbia**SUMMARY****Introduction/Objective** The percentage 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 the group of newborns conceived by ART in comparison to newborns conceived naturally (χ^2 test, $p = 0.0001$). 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 conceived spontaneously (χ^2 test, $p = 0.047$). There was no difference in the frequency of birth defects, genetic syndromes, and inborn errors of metabolism between the 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**INTRODUCTION**

According to the European Society of Human Reproduction and Embryology, from 1997 to 2014 there have been 1,478,452 newborns reported to be 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 is still much

perplexity in regard to the following questions: 'Does the (artificially) assisted reproduction represent greater risk for inadequate embryo development, poorer perinatal outcome?', 'What are the long-term consequences for the children?', as well as 'Are the risks equal for singleton 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 have been explained by the fact that the majority of pregnancies achieved by some of the medically assisted reproduction techniques were dominantly multiple pregnancies with additional risks of the mother's age and morbidity, therefore carrying higher risks of suboptimal fetal growth [4]. 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

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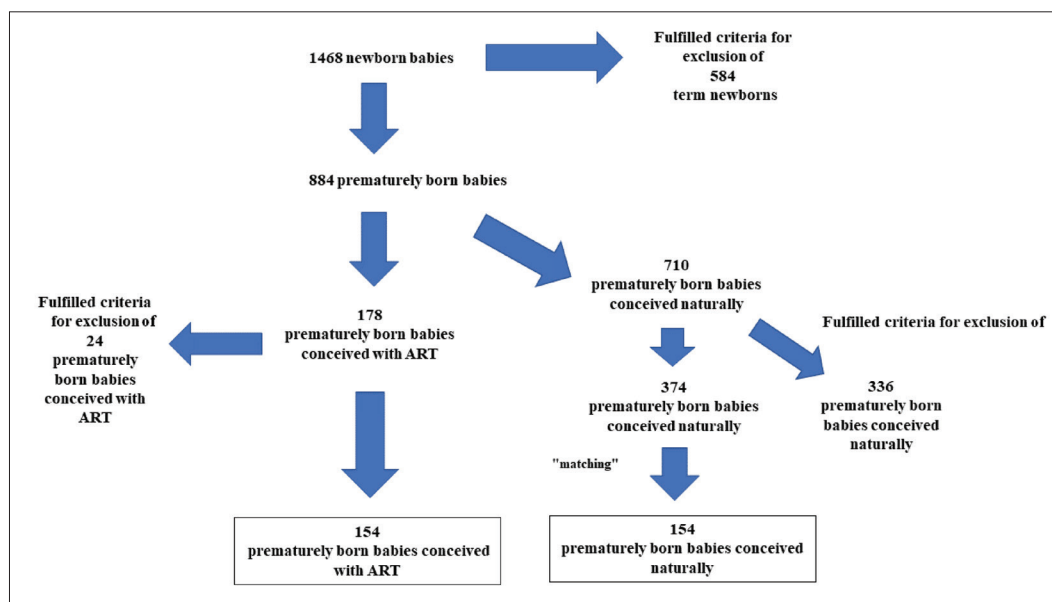


Figure 1. Algorithm for the selection of respondents included in the study

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, medicines, and other chemicals [3, 6]. Uteroplacental factors that negatively affect fetal growth and development are placental insufficiency, disorders of placentation and the occurrence of multiple pregnancies.

Regardless of causes, an infant born with ART is an 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 [7]. In spite of this, in Serbia and in the other regions of the former Yugoslavia, 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 singleton 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 Health Care of Children and Youth of Vojvodina in Novi Sad. The retrospective study included newborn babies born between January 1,

2011 and December 31 2012, treated at the Department. Data on the patients included in the retrospective part of the study were collected from medical records.

From this cohort, two groups were formed: the experimental group (Group 1) included all the 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 the 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 experimental group. Participants from both groups were matched according to gestational age (GA) and the date of birth. GA of the babies from the control group did 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 did not differ more than ± 3 months than that of the babies from the experimental group.

The 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 babies 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 the 3rd and 4th degree (as defined in the International Classification of Diseases – Tenth Revision (ICD-10) under code P52.2), 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 the Ethics Committee of the Institute of Health Care of Youth and Adolescents of Vojvodina.

RESULTS

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).

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).

The main characteristics of newborns from the groups are given in Table 1.

Table 1. The main characteristics of infants according to the group

Characteristic	Group 1 (n = 154)	Group 2 (n = 154)	p
GA ± SD (weeks)	31.829 ± 2.105	31.167 ± 2.138	0.152
Sex (female/male)	68/86	68/86	/
BW ± SD (g)	1537.516 ± 401.594	1924.6 ± 777.843	0.049
BL ± SD (cm)	41.255 ± 3.415	41.25 ± 3.536	0.992
HC ± SD (cm)	29.137 ± 1.686	29.547 ± 2.309	0.130
AS in 1st min. ± SD	5.712 ± 1.750	5.1667 ± 2.133	0.034
AS in 5th min. ± SD	7.307 ± 1.210	7.012 ± 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

There has been no statistically significant difference in infants between Group 1 and Group 2 according to GA and sex (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 from Group 1 and those from Group 2 was 59.427 g

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

Statistically, significantly there were more newborns with very low BW in Group 1 than in Group 2 (χ² test, p = 0.0001). The number of newborns with BW ≥ 2500 g was the same in both groups (χ² test, p = 0.702). There was no statistically significant difference in body length at birth and head circumference between newborns of the groups (Student's t-test, p = 0.992, p = 0.13).

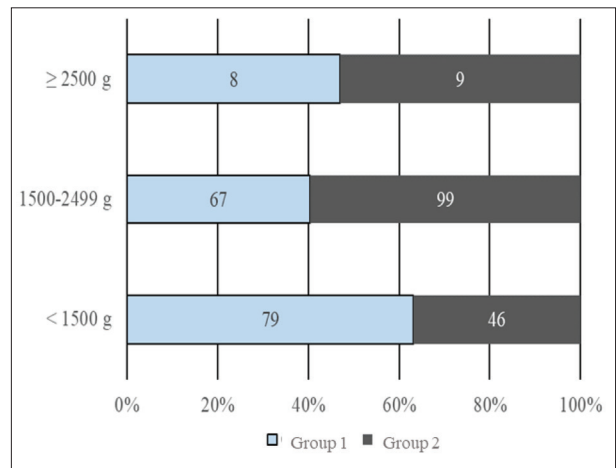


Figure 2. Proportion and absolute frequency of newborns of very low, low, and normal body weight in both groups of newborns

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

There was 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 was recorded.

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

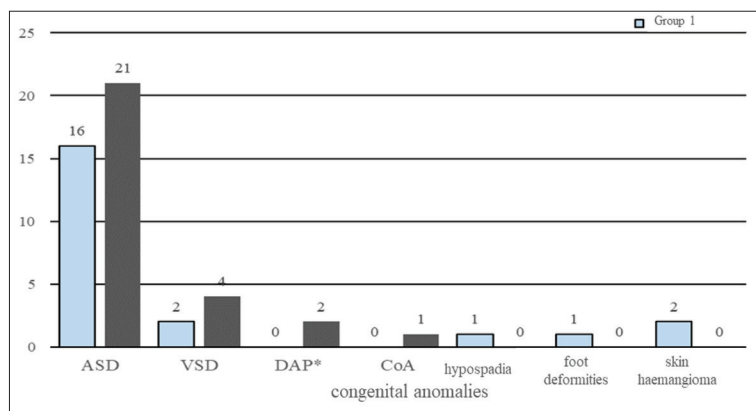


Figure 3. Structure of congenital anomalies and distribution of their absolute frequencies according to the groups of participants;

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

The average duration of hospitalization was statistically significantly shorter with newborns of Group 1 in comparison to those of Group 2. (Student's t-test, $p = 0.012$). The average duration of use of mechanical respiratory support was shorter in newborns of Group 1. The difference was 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 in those of 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 the groups (χ^2 test, $p = 0.354$).

The structure of congenital malformations and the distribution of their absolute frequencies according to the 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 the 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 ± 426.34 g.

Most of the studies carried out so far confirm these results. Results from a study by Lei et al. [8] showed that artificial conception increases the risk of LBW.

In a review article, Šljivančanin and Kontić-Vučinić [9] state that different studies' conclusion showed that infants from ART have significantly worse perinatal outcome (LBW, VLBW, SGA) compared with natural conception. This fact has also been confirmed in our research.

In a sample of our participants (Group 1), the value of AS in the first minute of life was statistically significantly higher than the value of AS in Group 2. In the studies available to us, lower values of AS in the first and fifth minute of life were most often reported for newborns conceived with ART [10, 11, 12]. The difference in 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 anticipated better and a 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 the following: length of hospitalization, duration of mechanical respiratory support, and the frequency of BPD and ROP. Infants conceived with ART had a spent less time on mechanical respiratory support and were discharged earlier from hospital (shorter hospitalization), and more often had BPD diagnosed. 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 is most likely the result of well-organized and comprehensive monitoring of ART-initiated pregnancies (regular examinations, expert ultrasound, etc.). In contrast to our results, Giorgione et al. [13] concluded that fetuses conceived with IVF/ICSI methods are at an increased risk of developing congenital heart defects compared with those conceived spontaneously.

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, 14, 15]. Disagreement exists in the results that refer to the frequency of BPD and ROP. In a study conducted by Corchia et al. [16], 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. Also, unlike our study, the study by Corchia et al. [16] 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, other studies found an increased incidence of both BPD and ROP in babies who were conceived by IVF [15, 17].

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 [17, 18].

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 [17]. However, the prolonged lockdown of health services providing fertility treatments might be detrimental for society as a whole, and infertility patients in particular [19].

These are new challenges in the field of reproductive medicine, which leads to further research regarding characteristics and morbidity of newborns conceived with ART 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 ROP, which occurs more often in prematurely born newborns conceived naturally. Lower BW and IUGR are potential risk factors for poorer postnatal outcome in newborns from pregnancies conceived with ART. AS in the first 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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Conflict of interest: None declared.

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Карактеристике и морбидитет превремено рођене новорођенчади зачете вантелесном оплодњом

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САЖЕТАК

Увод/Циљ Процент живорођене новорођенчади зачете неком од метода вантелесне оплодње (асистирани репродуктивне технологије) у сталном је порасту. У неким европским земљама досеже и 6%. У Србији је он нешто виши од 1%. Циљ рада је био да се анализирају карактеристике и морбидитет превремено рођене новорођенчади зачете асистираним репродуктивном технологијом.

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

Резултати У овом истраживању било је статистички значајно више новорођенчади са врло малом порођајном масом у групи новорођенчади зачете асистираним репродуктивном

технологијом у односу на новорођенчад из спонтано зачелих трудноћа (χ^2 тест, $p = 0,0001$). Стопа морбидитета превремено рођене деце зачете вантелесном оплодњом није већа у односу на превремено рођену децу зачету природним путем. Бронхопулмонална дисплазија (χ^2 тест, $p = 0,006$) јавља се чешће код деце зачете вантелесном оплодњом, а ретинопатија прематуритета (χ^2 тест, $p = 0,047$) јавља се 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 интраутерини застој раста су могући фактори ризика за лошији постнатални исход код новорођенчади зачете асистираним репродуктивном технологијом.

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