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COMPARATIVE CHARACTERISTICS OF THE PERINATAL PERIOD AMONG CHILDREN BORN IN THE EARLY STAGES OF GESTATION USING ASSISTED REPRODUCTIVE TECHNOLOGIES AND SPONTANEOUS PREGNANCY COURSE

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Abstract. A retrospective study was conducted of 42 copy pairs of newborns born in St. Petersburg and the Leningrad region as a result of independent pregnancy and after the use of ART at 22 weeks. 0 days — 27 weeks. 6 days inclusive for the period 2018–2022 as a result of a singleton or multiple pregnancy (twins). Also, each group was divided into 2 subgroupsmore, according to gestational age. All 4 subgroups were compared with each other. Based on the study, it can be noted that the course of pregnancy and childbirth in children of the compared groups is ambiguous. Nevertheless, there is unity in the implementation of biological programs of growth and development, as well as a significantly low level of somatic and reproductive health in mothers who planned pregnancy using ART. It is planned to create an evidence-based algorithm that will help practicing doctors and future parents avoid undesirable consequences and minimize the risks to the life and health of newborns.

Keywords*: assisted reproductive technologies, deeply premature babies, premature birth, infertility, mortality of newborns*

СРАВНИТЕЛЬНАЯ ХАРАКТЕРИСТИКА ТЕЧЕНИЯ ПЕРИНАТАЛЬНОГО ПЕРИОДА ДЕТЕЙ, РОЖДЕННЫХ НА РАННИХ СРОКАХ ГЕСТАЦИИ, С ИСПОЛЬЗОВАНИЕМ ВСПОМОГАТЕЛЬНЫХ РЕПРОДУКТИВНЫХ ТЕХНОЛОГИЙ И САМОСТОЯТЕЛЬНОЙ БЕРЕМЕННОСТИ

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Резюме. Проведено ретроспективное исследование 42 пар-копий новорожденных детей, рожденных в Санкт-Петербурге и Ленинградской области в результате самостоятельной беременности и после приме-

нения вспомогательных репродуктивных технологий (ВРТ) на сроке 22 недель 0 дней — 27 недель 6 дней включительно за период 2018–2022 гг. в результате одноплодной или многоплодной беременности (двойни). Каждую группу разделили также на еще 2 подгруппы по срокам гестации. Сравнивались все 4 подгруппы между собой. На основании проведенного исследования можно отметить неоднозначность течения беременности и родов у детей сравниваемых групп. Тем не менее отмечается единство в реализации биологических программ роста и развития, а также достоверно низкий уровень соматического и репродуктивного здоровья у матерей, планировавших беременность при помощи ВРТ. Готовится создание доказательного алгоритма, который поможет практикующим докторам и будущим родителям избежать нежелательных последствий и минимизирует риски для жизни и здоровья новорожденных.

Ключевые слова: *вспомогательные репродуктивные технологии, глубоко недоношенные дети, преждевременные роды, бесплодие, летальность новорожденных*

INTRODUCTION

After a short period of increasing birth rates in 2010–2017, a decline began again, associated with the generation born in the 1990s entering childbearing age. Similar trends as in the Russian Federation (RF) emerged in St. Petersburg, which required the adoption of serious government decisions in the area of improving women's and children's health. The President of the Russian Federation and the Government of Russia adopted enhanced measures of social support for those in need under the large-scale projects "Healthcare" and "Demography", which provide for accelerated construction of schools and preschool institutions [12].

At the same time, one of the problems in both the medical and social spheres remains infertility. In the context of a difficult demographic situation, the use of all resources to increase the birth rate becomes an important factor. If there is no effect of treatment for infertility within a year, methods of assisted reproductive technologies (ART) can be offered, which involve not only the onset of pregnancy, but also nursing of babies [9].

Currently, the number of births as a result of ART is increasing and reaches 2,7% (data from the ART registry report of the Russian Association of Human Reproduction (RAHR) for 2021). According to operational data from the Organizational and Methodological Center for Analysis and Forecasting of Maternal and Child Health of the Health Committee of St. Petersburg, the number of children born using ART in 2023 was more than 5%.

According to the data, presented by Christine Wyns on July 5–8, 2020 at the European Society of Human Reproduction and Embryology (ESHRE 2020) Annual Meeting, Russia ranks first in the number of cycles of ART performed (137,211). In previous years, according to RAHR, more than 1,5 million treatment cycles were carried out.

In Russia, the use of ART is regulated by Federal Law No. 323-FZ "On the fundamentals of health protection of citizen of the Russian Federation" (Chapter 6, Article 55) dated November 21, 2011 and orders of the Ministry of Health of the Russian Federation dated August 30, 2012 No. 107n (as amended on February 1, 2018) "On the procedure for the use of assisted reproductive technologies, contraindications and restrictions on their use", as well as "On approval of the standard of medical care for infertility using assisted reproductive technologies" dated October 30, 2012 No. 556n.

Along with the problems of the birth rate, the issue of nursing and rehabilitation of extremely premature babies is no less acute. According to the clinical practice guidelines "Preterm births", published in the letter of the Russian Ministry of Health dated December 17, 2013 No. 15-4/10/2-9480, "the frequency of premature births in developed countries is 5–7%, neonatal mortality is 28%. About 15 million premature babies are born in the world every year. Preterm births (PB) are a complex medical and social problem associated with solving the problems of improving the subsequent quality of life of children born prematurely, and are associated with material and economic costs".

As it is known, the severity of complications associated with prematurity is inversely proportional to the gestational age [14]. The need to prolong pregnancy, as well as improve the care of deeply premature babies at all stages, have determined the need for more careful monitoring of expectant mothers, especially those who are planning pregnancy using ART methods. It has also been established that multiple pregnancies after in vitro fertilization (IVF) are considered a high-risk group for the development of perinatal pathology in the newborn, caused not only by prematu-

rity, but also by the diseases that the mother has and caused infertility [7].

AIM

The aim of the study is to compare, according to certain criteria, the health status of neonates born at early term gestation, after assisted reproductive technologies and during spontaneous pregnancy

MATERIALS AND METHODS

A retrospective, observational, prolonged (at the time of hospitalization) study was conducted of 42 pairs of newborn children born in St. Petersburg and the Leningrad region as a result of spontaneous pregnancy and after the use of ART at a period of 22 weeks 0 days — 27 weeks 6 days inclusive for the period 2018–2022 as a result of singleton or multiple pregnancies (twins). Of these, 11 infants in each group were born at a very early stage (22–24 weeks), 31 children were born at early term gestation (25–27 weeks). All 4 subgroups were compared with each other. The obtained data were analyzed using the IBM SPSS Statistics v.26 statistical program and the WinPepi additional counting program. Categorical variables are presented as absolute values (n) and their sample proportion (%). Quantitative variables are represented either by the mean and its standard deviation (M±SD) or by the median (Me) with the 1st and 3rd quartiles ([Q1; Q3]). To compare the frequency characteristics of qualitative variables, the Fisher's exact test (F) and Pearson's chi-squared test (χ^2) were used; to compare quantitative variables, nonparametric comparison methods the Kruskal–Wallis (KW) or Mann–Whitney (U) were used at the null hypothesis rejection level of $p < 0,05$.

The following criteria of comparison were used in the work: anthropometric data of the child at birth, scales predicting the condition of newborns, somatic diseases of the mother, obstetric history of the mother, blood tests at birth (including an arterial blood gas test), blood oxygen level, treatment carried out both in the maternity hospital and in the hospital, examinations of the infant during hospitalization, diseases of the child at the time of discharge from the hospital, weight upon transfer to the department of neonatal pathology and weight at discharge, outcome. A total of 100 criteria.

Exclusion criteria: babies born to mothers with alcohol or drug abuse; children born through surrogacy, egg or sperm donation (when the donor was not a spouse); infants whose mothers suffered from a severe viral infection during pregnancy (for example, COVID-19); children from mothers with viral hepatitis B, C, HIV; children from multiple pregnancies (triplets); children with hereditary diseases and severe congenital malformations.

RESULTS

In recent years, the problem of preserving the life and health of premature infants with extremely low birth weight (ELBW) has become especially acute in our country due to the improvement of nursing technologies for this category, as well as the introduction of new live birth criteria in the Russian Federation recommended by WHO [13]. The incidence of premature births in the world in recent years has been 9,5%, with 15,000,000 premature babies born annually and, despite the emergence of new technologies, it is not decrea-

Table 1. Quantitative characteristics of the surveyed groups

Таблица 1. Количественные характеристики обследованных групп

Сроки гестации (Gestation period) / Критерии (Criteria)	22–24 нед/wg	25–28 нед/wg	Одноплодная беременность / Singl pregnancy	Многоплодная беременность/ Twin pregnancy	Пол / Sex		Исход / Outcome	
					ж/f	м/m	выписан/ discharged	ЛИ / LO
СБ / SP, n (%)	11 (26,2)	31 (73,8)	19 (45,3)	23 (54,8)	22 (52)	20 (48)	34 (81)	8 (19)
ВРТ / ART, n (%)	11 (26,2)	31 (73,8)	15 (35,7)	27 (64,3)	24 (57)	18 (43)	31 (73,8)	11 (26,2)
Всего / Total, n (%)	22 (26,2)	62 (73,8)	34 (40,5)	50 (59,5)	46 (55)	38 (45)	65 (77,4)	19 (22,6)

Примечание: ВРТ — вспомогательные репродуктивные технологии; ЛИ — летальный исход; СБ — самостоятельная беременность.
Note: ART — assisted reproductive technologies; LO — letal outcome; SP — spontaneous pregnancy.

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Table 2. Maternal morbidity

Таблица 2. Заболеваемость матерей

Критерии / Criteria	Тест / Test	p
1. Заболевания репродуктивной сферы / Diseases of the reproductive sphere	χ^2	0,032
2. Заболевания эндокринной системы / Diseases of the endocrine system	F	0,000
3. Заболевания острыми респираторными вирусными инфекциями / Acute respiratory diseases	F	0,036
4. Заболевания органов кровообращения / Diseases of the circulatory system	χ^2	0,313
5. Заболевания органов желудочно-кишечного тракта / Diseases of the gastrointestinal tract	χ^2	0,051
6. Заболевания органов мочевыделительной системы / Diseases of the urinary system	χ^2	0,609
7. Болезни глаз и придаточного аппарата / Diseases of the eye and appendage	χ^2	0,058
8. Заболевания, передающиеся половым путем / Sexually transmitted diseases	χ^2	0,322
9. Заболевания нервной системы / Diseases of the nervous system	χ^2	0,500
10. Гестационный сахарный диабет / Gestational diabetes mellitus	χ^2	0,260

sing [14]. In developed countries, it is increasing, primarily as a result of the use of new reproductive technologies [18]. About 5% of them occur before 28 weeks [16].

Perm scientists have found that every third child born as a result of assisted medical technologies is premature (32%). The main factors influencing the birth of a preterm infant in IVF pregnancies are: maternal age over 35 years, duration of infertility and a history of miscarriage [5].

When assessing the development and condition of babies born as a result of the use of ART, some contradictions have arisen. Until now, experts of different medical specialties (embryologists, neonatologists, psychologists) have not come to a consensus regarding the prediction of health and quality of life of this group of children.

Due to the fact that, as a rule, ART is performed in centers that are separated from the antenatal clinic where the woman is subsequently observed, healthcare facilities where the delivery occurs, and clinics where children are observed in the coming years, and also the fact that 63% of parents conceal the method of pregnancy, it is practically impossible in the Russian Federation to obtain reliable information about the health of children born after ART [8].

In connection with the ambiguity of estimates of the health and development of children conceived by ART and usually carried out without strict parallel control, certain doubts arise about the equivalence of biological processes in naturally conceived babies and children conceived through ART.

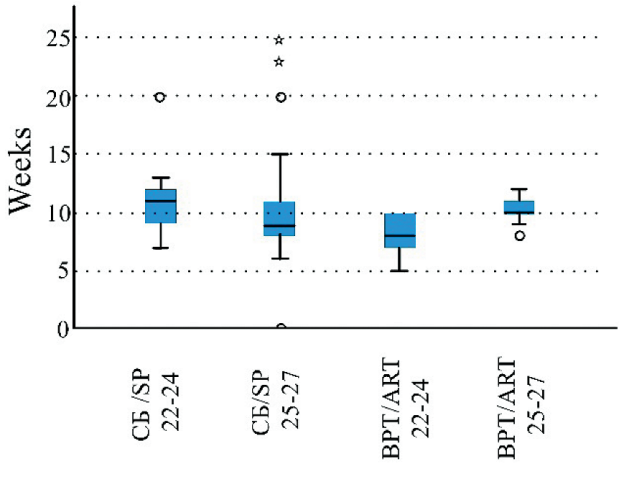

Fig. 1. Registration in the women's consultation

Рис. 1. Постановка на учет в женскую консультацию

The scientific work plans to show the importance of assessing children's development using the randomization method, namely, distribution by development conditions (pairwise selection, the "copy-pair" method) in order to minimize differences in the pre-, intra-, and postnatal periods of development of infants born in the early stages of gestation.

Table 1 presents the design of the study. Children were selected using the "copy-pair" method by gestation period, place of birth and nursing (St. Petersburg and the Leningrad Region), maximally matched by sex and number of fetuses (single or twin pregnancy).

Initially, ART methods were used to overcome reproductive problems associated with obstruction or absence of fallopian tubes. Currently, the

Table 3. Comparative anthropometry data with glow

Таблица 3. Сравнительные данные антропометрии при рождении

Критерии / Criteria	Масса / Weight		Рост / Height		Окружность головы / Circle heads		Окружность груди / Circle breast	
	СБ / SP	ВРТ / ART	СБ / SP	ВРТ / ART	СБ / SP	ВРТ / ART	СБ / SP	ВРТ / ART
M (±SD)	792±145	746±145	531±2	31±3	23±4	23±2	21±2	21±2
Me	790	750	31	32	23	23	21	21
[Q1; Q3]	[680; 900]	[670; 860]	[30; 33]	[29; 33]	[22; 25]	[22; 25]	[22; 25]	[19; 22]
U/P	745/0,220		555,5/0,975		842,0/0,861		818,0/0,833	

Примечание: ВРТ — вспомогательные репродуктивные технологии; СБ — самостоятельная беременность (здесь и далее в таблицах).
Note: ART — assisted reproductive technologies; SP — spontaneous pregnancy (here and further in the tables).

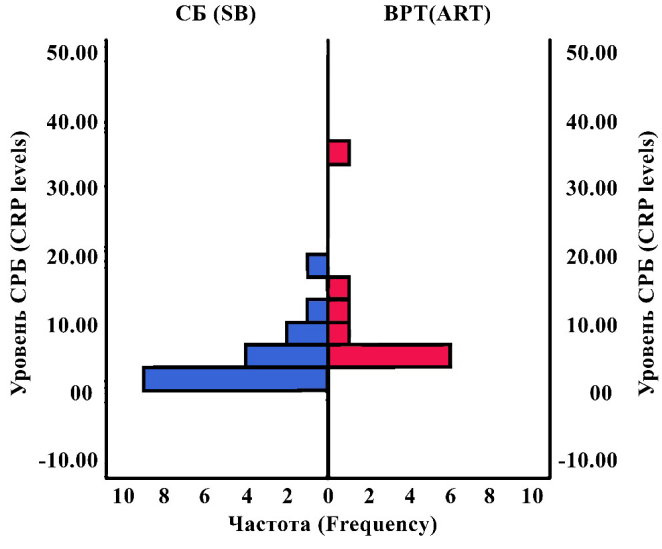

Fig. 2. Comparison of C-reactive (CRP) protein levels in newborns with assisted reproductive technologies (ART) and spontaneous pregnancy (SP)

Рис. 2. Сравнение уровня С-реактивного белка (СРБ) у новорожденных при вспомогательных репродуктивных технологиях (ВРТ) и самостоятельной беременности (СБ)

indications for the use of these methods are much broader and include various causes of infertility: endocrine, idiopathic, male factor, etc. However, the maternal health is extremely important for the future child. Most women who have resorted to ART are in the high-risk group for complicated pregnancy and childbirth, which adversely affects the intrauterine development of the fetus [17]. The health status of mothers undergoing ART and mothers who became become pregnant naturally at the time of conception and during pregnancy differ; the results are shown in Table 2.

According to the data in Table 2, diseases of the endocrine system, reproductive sphere and acute respiratory diseases are higher in mothers whose babies were born through ART. The total number of diseases in mothers in the ART group is also higher (p=0,032). Antibiotic therapy was used significantly more often in pregnant women after ART (p=0,004).

According to the chart (Fig. 1), mothers whose children were born using ART at an extremely early stage were registered with antenatal clinics earlier than others (p=0,019).

Modern studies devoted to the evaluation of long-term results are ambiguous and often contradictory. Most studies do not show significant differences between infants depending on the method of conception [8, 21]. At the same time, the need for a more in-depth study of this issue is recognized, and it is also important to research the general functioning of the family system in the case of ART before making final conclusions [22].

The study did not reveal reliable differences in the assessment of anthropometric data in newborns in the comparison groups. The Apgar scores of neonates born early term gestation in the compared groups did not reveal reliable differences (p> 0,05 at all stages of assessing the condition

of newborns; Apgar1 p = 0,225; Apgar2 p = 0,418; Apgar3 p = 0,507).

The prenatal period can be used to judge both the effectiveness of ART and the adequacy of fetal development. Factors influencing pregnancy outcome include the use of stimulating hormones, changes in hormone levels, temporary presence of gametes outside the woman's body, the frequency of in vitro fertilization (IVF) and the woman's somatic condition, the impact of environmental factors on the mother and fetus during intrauterine development, methods of delivery and social factors [10].

Some authors claim that the use of ART increases the miscarriage rates, which may affect the further development of children [1, 3].

According to the research conducted by G.U. Asymbekova et al. (2014), in the group of women with ART, it was more common to resort to operative delivery, since the probability of diseases and the risk of complications are higher for them than for women with spontaneous pregnancy [2]. The author's work also obtained data showing that operative delivery at an early stage of gestation is significantly more often used for mothers after ART (p = 0,024).

Table 4. Treatment in the early postnatal period

Таблица 4. Лечение в раннем постнатальном периоде

Критерии / Criteria	СБ / SP Me [Q1; Q3]	ВРТ / ART Me [Q1; Q3]	Тест	P
1. Искусственная вентиляция легких (дни) / Mechanical ventilation (days)	23 [7; 38]	20 [8; 39]	U=613,000	0,854
2. Кислородная зависимость (дни) / Oxygen dependency (days)	69 [59; 90]	78[57; 94]	U=593,000	0,529
3. Переход на полное энтеральное питание (дни) / Transition to full enteral nutrition (days)	49 [24; 83]	45 [23; 70]	U=439,000	0,440
4. FiO_2 max роддом / FiO_2 max maternity hospital	0,60 [0,40; 0,80]	0,50 [0,40; 0,70]	U=749,500	0,232
5. FiO_2 min роддом / FiO2 min maternity hospital	0,25 [0,21; 0,30]	0,25 [0,21; 0,30]	U=838,500	0,685
6. FiO_2 в стационаре / FiO_2 in the hospital	0,34 [0,30; 0,45]	0,35 [0,30; 0,45]	U=909,500	0,655
7. Сурфактант (количество) / Surfactant (quantity)	1 [1; 2]	2 [1; 2]	U=950,500	0,496

Критерии / Criteria	Количество человек / Number of people n (%)	Количество человек / Number of people n (%)	Тест	p
1. Инотропная терапия (адреналин) / Inotropic therapy (adrenaline)	13 (31%)	13 (31%)	χ^2=0,000	0,593
2. Инотропная терапия (дофамин) / Inotropic therapy (dopamine)	20(47,6%)	14(33,3%)	χ^2=1,779	0,133
3. Инотропная терапия (добутамин) / Inotropic therapy (dobutamine)	34(81%)	34(81%)	χ^2=0,000	0,609
4. Гормональная терапия / Hormone therapy	26(61,9%)	20(47,6%)	χ^2=1,730	0,136
5. Противосудорожная терапия / Anticonvulsant therapy	5(12,2%)	3(7,3%)	χ^2=0,554	0,356
6. Обезболивание (фентанил) / Anesthesia (fentanyl)	20(47,6%)	16(38,1)	χ^2=0,778	0,254
7. Атибактериальная терапия / Antibacterial therapy	42(100%)	42(100%)	Не применимо / Not applicable	Не применимо / Not applicable

Table 5. Pairwise comparison of mortality of children born in the early stages during ART and from independent pregnancy

Таблица 5. Попарное сравнение летальности детей, рожденных на ранних сроках при ВРТ и от самостоятельной беременности

Общий фактор / Common factor χ^2		СБ / SP (22–24)		СБ / SP (25–27)		ВРТ / ART (22–24)		ВРТ / ART (25–27)	
		p	χ^2	p	χ^2	p	χ^2	P	
Сроки гестации (нед) / Gestation period (weeks of gestation)	СБ / SP (22–24)			0,004	0,949	2,959	0,085	0,170	0,680
	СБ / SP (25–27)	0,004	0,949			6,002	0,014	0,465	0,495
	ВРТ / ART (22–24)	2,959	0,085	6,002	0,014			8,912	0,003
	ВРТ / ART (25–27)	0,170	0,680	0,465	0,495	8,912	0,003		

However, it is known that the risk of infectious complications during operative delivery is 2,8 times higher compared to vaginal delivery [22]. Numerous scientific studies demonstrate that children born as a result of operative delivery, have an increased risk of allergic and autoimmune diseases, type 1 diabetes mellitus and obesity in the future, which dictates the obstetrician-gynecologist to take a more rational approach to the choice of the method of delivery [20, 21].

C-reactive protein (CRP) level in children born through ART is shown in Fig. 2, which indicates a more pronounced inflammatory process in children born after ART (p=0,04). Other blood parameters in this study did not reveal any significant difference.

Table 4 shows that there is no significant difference in the management of children born at an early stage of gestation in a maternity hospital and in the intensive care unit of a hospital. The treatment methods used corresponded to the recommendations for the care of newborns with respiratory distress syndrome [4].

Despite the fact that mothers of children born through ART were registered at antenatal clinics at a reliably early period, the mortality rate of these newborns is higher than in the other groups p=0,003 (Table 5).

In this work, no significant differences were found in anthropometric data or in the tactics of managing children in the study groups and those born at early term gestation. In the maternity hospital and intensive care unit of the hospital, treatment was consistent with clinical practice guidelines for management extremely low birth weight infants, as well as with protocols for providing medical care to this category of neonates. However, further in-depth research is required to identify the causes of perinatal mortality in children born at a very early stage (22–24 weeks), p=0,003 (Table 5) after the use of ART, taking into account their significant early registration at antenatal clinics.

DISCUSSION

The conducted research revealed a number of organizational factors that substantially complicated the work. Firstly, the lack of special document labeling of pregnant women and children born using ART entailed significant searches: doses of estrogens, the number of cycles of maintenance therapy, etc. This was accompanied by negativism of mothers who did not want to communicate on infertility and the methods of its treatment that were used in each particular case.

The data from the performed work showed unity in the implementation of biological programs of growth and development, as well as a significantly lower level of somatic and reproductive health in mothers who planned pregnancy using ART. In addition, the pregnancy of expectant mothers more often occurred against the background of infectious diseases, which required the appointment, possibly due to greater immunodeficiency, of antibacterial therapy.

The high CRP level in children of the ART group at birth (p = 0,040) to a certain extent confirms the presence of intrauterine infection [11]. Delivery of women in this group was carried out surgically (p = 06024), since the probability of diseases and high risk of complications in them is higher than in women with spontaneous pregnancy [15].

Treatment of newborns at the stage of the maternity hospital and intensive care unit did not differ significantly. At the same time, children born after ART at a very early gestational age (22–24 weeks) died significantly more often, which is most likely a reliable sign in favor of reduced adaptive capacities in babies conceived by ART. Almost all of the deceased were diagnosed with intrauterine infection.

In order to reduce the risk of adverse perinatal outcomes, it is necessary to structure obstetric-gynecological, neonatal and pediatric counseling in families planning ART at the outpatient stage [8].

CONCLUSION

Thus, based on the conducted study, it can be noted that the course of pregnancy and childbirth in infants of the comparison groups is ambiguous. Extremely premature babies are at high risk of infectious complications, which sharply reduces their adaptive capacities. Modern studies are unanimous in their opinion about the predominantly ascending route of infection in case of intra-amniotic infection [6]. Obstetric problems associated with ART are primarily due to the age of the mother, the presence of extragenital pathology. The most significant risk is multiple pregnancy, which should be avoided, since in this case the situation can become difficult to manage [19]. The high risk of death or development of complications will apparently require new recommendations for pregnancy registration, its management and providing medical care to newborns. A logical and relevant solution to the problem may be the creation of ART registries [23].

These results showed only some differences between the groups of children. In order to identify risk groups and determine the correct medical tactics, it is planned to create an evidence-based algorithm that will help practicing doctors and future parents avoid undesirable consequences and minimize the risks to the life and health of newborns.

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