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POSITIVE AND NEGATIVE CONSEQUENCES OF THE MENTAL DEVELOPMENT OF CHILDREN CONCEIVED USING ASSISTED REPRODUCTIVE TECHNOLOGIES

CONSECUENCIAS POSITIVAS Y NEGATIVAS DEL DESARROLLO MENTAL DE LOS NIÑOS CONCEBIDOS MEDIANTE TECNOLOGÍAS DE REPRODUCCIÓN ASISTIDA

CONSEQUÊNCIAS POSITIVAS E NEGATIVAS DO DESENVOLVIMENTO MENTAL DE CRIANÇAS CONCEBIDAS POR MEIO DE TECNOLOGIAS DE REPRODUÇÃO ASSISTIDA

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Palabras Clave: tecnologías de reproducción asistida, fertilización in vitro, niños y adolescentes, desarrollo psicofísico.

Palavras-chave: tecnologias de reprodução assistida, fertilização in vitro, crianças e adolescentes, desenvolvimento psicofísico.

A B S T R A C T

The article is devoted to the analysis of the mental development of children conceived using assisted reproductive technologies. The main results of a study conducted within the framework of the scientific theme of the Federal State Budgetary Institution "Research Center for Mental Health" are presented. The study was conducted using the Wechsler test and neuropsychological examination. The study involved 110 ART children and 104 children with natural conception (control group) aged 3 to 15 years. The groups are similar in sociodemographic and mental health parameters. A brief excursion into the history of the application of the method and research related to the assessment of offspring born through ART is given. We note and discuss the obvious "advantages" of using assisted reproductive technologies: solving the problems of infertile couples in the desire to have their own children, more care for children born through ART, an increase in the number of additional classes, etc., which are carried out with children for their comprehensive development or correction of problematic situations. The obvious "disadvantages" or limitations of the use of ART are also considered, such as: high incidence of perinatal pathology compared to the group of natural conception; a significant deficit in the neurodynamic (energy) component of activity and a number of other neuropsychological factors, which is more represented in the ART group, etc. Features in ART children - the variety of IQ levels is wider than in children of the control group, we observe various neurodeficiencies in children of the control group and ART. The authors propose new directions for their research for the future, related to possible limitations in the use of ART, such as: the age of the parents, multiple pregnancies and the characteristics of the ART procedure itself.

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R E S U M E N

El artículo está dedicado al análisis del desarrollo mental de los niños concebidos mediante tecnologías de reproducción asistida. Se presentan los principales resultados de un estudio realizado en el marco del tema científico de la Institución Presupuestaria del Estado Federal "Centro de Investigación sobre Salud Mental". El estudio se realizó mediante la prueba de Wechsler y un examen neuropsicológico. En el estudio participaron 110 niños con ART y 104 niños con concepción natural (grupo de control) de edades comprendidas entre 3 y 15 años. Los grupos son similares en parámetros sociodemográficos y de salud mental. Se ofrece una breve excursión a la historia de la aplicación del método y las investigaciones relacionadas con la evaluación de la descendencia nacida mediante ART. Observamos y discutimos las "ventajas" obvias del uso de tecnologías de reproducción asistida: solución de los problemas de las parejas infértiles en el deseo de tener sus propios hijos, mayor atención a los niños nacidos mediante ART, aumento del número de clases adicionales, etc. las cuales se realizan con los niños para su desarrollo integral o corrección de situaciones problemáticas. También se consideran las obvias “desventajas” o limitaciones del uso de ART, tales como: alta incidencia de patología perinatal en comparación con el grupo de concepción natural; un déficit significativo en el componente neurodinámico (energía) de la actividad y una serie de otros factores neuropsicológicos, que está más representado en el grupo ART, etc. Características en los niños ART: la variedad de niveles de coeficiente intelectual es más amplia que en los niños del grupo de control , observamos diversas neurodeficiencias en niños del grupo de control y ART. Los autores proponen nuevas direcciones de investigación para el futuro, relacionadas con posibles limitaciones en el uso de la ART, tales como: la edad de los padres, los embarazos múltiples y las características del procedimiento de ART en sí.

R E S U M O

O artigo é dedicado à análise do desenvolvimento mental de crianças concebidas com o uso de tecnologias de reprodução assistida (TRA). São apresentados os principais resultados de um estudo realizado no âmbito do tema científico da Instituição Orçamentária do Estado Federal "Centro de Pesquisa em Saúde Mental". O estudo foi conduzido utilizando o teste de Wechsler e uma avaliação neuropsicológica. A pesquisa envolveu 110 crianças concebidas por TRA e 104 crianças de concepção natural (grupo de controle) com idades entre 3 e 15 anos. Os grupos são semelhantes em parâmetros sociodemográficos e de saúde mental. É apresentada uma breve incursão na história da aplicação do método e pesquisas relacionadas à avaliação da prole nascida por meio de TRA. Notamos e discutimos as evidentes “vantagens” do uso de tecnologias de reprodução assistida: a resolução de problemas de casais inférteis que desejam ter filhos próprios, maior cuidado com as crianças nascidas por TRA, aumento do número de aulas adicionais, etc., que são realizadas com as crianças para seu desenvolvimento abrangente ou para correção de situações problemáticas. Também são considerados os evidentes “desvantagens” ou limitações do uso de TRA, tais como: alta incidência de patologias perinatais em comparação com o grupo de concepção natural; um déficit significativo no componente neurodinâmico (energético) da atividade e em vários outros fatores neuropsicológicos, que estão mais presentes no grupo TRA, entre outros. Em crianças concebidas por TRA, observa-se uma maior variação nos níveis de QI em comparação com crianças do grupo de controle, além de diversos déficits neuropsicológicos em ambos os grupos. Os autores propõem novas direções para pesquisas futuras, relacionadas a possíveis limitações no uso de TRA, como a idade dos pais, gravidezes múltiplas e as características do próprio procedimento de TRA.

The issues of reproduction of healthy generations have always been urgent, they have become especially important against the background of declining birth rate, increasing number of men and women with infertility. From the end of the 19th century to the beginning of the 20th century, assisted reproductive technologies (ART) have been increasingly successfully improved and applied.

reproductive technologies (ART), initially used for work with animals, and only then used for treatment of various types of human infertility [1-3]. ARTs currently include the following: in vitro fertilization (IVF), where fertilization occurs by placing sperm and eggs in a petri dish; Intraplasmic sperm injection (ICSI), when fertilization occurs by placing selected sperm directly into the cytoplasm of the egg. Surrogacy, donation of reproductive material and other methods of human reproduction are actively used in Russia. In terms of frequency of use, the IVF method takes the leading position, followed by the ICSI method, which allows you to increase the chances of successful conception. The use of cryobanking or cryopreservation (freezing of

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fertilized eggs in liquid nitrogen) allows storing human embryos for a long time and later using unfrozen material for artificial insemination [4].

In the early 1990s Russia entered a period of prolonged depopulation, in this regard, the question arises about possible options to help infertile couples and, in general, people with reproductive health problems, both men and women. The WHO's position is well known that if the infertility rate in a country exceeds 15%, the problem reflects not only medical issues, but also socio-demographic issues. It is not by chance that scientists who participated in the realization of the first act of successful IVF in 1978, many years later received the Nobel Prize [5].

The data provided by the Scientific Center of Obstetrics and Gynecology of the Ministry of Health of the Russian Federation show that in Russia today 7-8 million Russian women and 3-4 million men are infertile, and in the structure of infertility up to 45% of infertility falls to the share of women and 40% to the share of men, although in relation to men the data should be clarified [6].

Thus, the problem of application of various assisted reproductive technologies is urgent and in demand both in science and in practice ones.

In the practical implementation of ART, future parents are always deeply interested in the issue of risks for both the health of the mother and the future offspring, possible "pros" and "cons" of these procedures both in the short and long term.

A number of domestic and foreign researchers don't exclude that children conceived with the help of modern ART may have abnormalities in the state of physical development. Describing the possible risks of ART, the authors note the following probable factors of negative impact on the subsequent psychomotor, speech and cognitive development of a child conceived through IVF, ICSI and other ART: multiple pregnancies, chronic diseases of the mother, genetic diseases, perinatal hazards, low weight and prematurity; the contribution of the family situation (upbringing, child-parent relations, psychological and pedagogical support of children's development at all age stages, etc.) is also significant. Many domestic and foreign researchers don't exclude that children conceived with the help of modern ART may have deviations in the state of physical development, but a direct link between such peculiarities of development directly with the type, quality and quantity of ART used has not been proven, although there are assumptions about the complex origin of these deviations, which are associated with aggravating prenatal and postnatal specifics (multiple births, prematurity, low birth weight, etc.). [1, 7, 8], the contribution of the family situation (upbringing, child-parent relations, psychological and pedagogical support of children's development at all age stages, etc.) is also significant. [4, 7, 9, 10, 11, 12, 13]

Analysis of the literature shows that researchers of IVF children's development focus mainly on anthropometric, motor, less often speech and emotional parameters, cognitive indicators are rarely considered, mainly in the assessment of school success.

In this regard, the study we are conducting has a certain novelty both in terms of the subject matter and methodology, providing a multidisciplinary approach to the study and analysis the problem of cognitive and emotional-personal development of children born with IVF [2, 7, 8, 14].

Following the authors, it is possible to distinguish the following directions of research into the study of possible negative consequences and risks of IVF:

Medical: mainly physiological assessment of IVF children is carried out, many "minuses" in development are obtained, which are often leveled with age, psychophysical and speech development may be delayed, there are more risks of development in the following years of various deviations; multiple pregnancy and in general perinatal pathology, pathologically flowing pregnancy are of importance.

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Thus, the main risks are related to perinatal period, the consequences of hypoxia, etc., the health and age of the mother, and the peculiarities of the ART itself [14, 15].

Psychological subject of study is the psychological state of the expectant mother, the analysis concerns her mental state, psychological readiness for motherhood, etc.; studies of children are conducted mainly in infancy, early childhood and preschool age, rarely an integral assessment of IVF child development is carried out. The key outcome of most studies, the main conclusion is that IVF children are the same as children with natural conception [16].

A small number of works discuss the problem of attachment of "test tube children", family situation [17, 18]

The scientific theme that has been conducted at FSBSI MHRC since 2019 is aimed at analyzing the mental development (cognitive emotional-personal) of children conceived with ART who crossed the threshold of infancy and early childhood.
Goal: To assess the mental development (IQ and neuropsychological status) of children conceived using assisted reproductive technologies in comparison with children with natural conceived.

MATERIAL AND METHODS

Methods. Analysis of anamnestic data; Wechsler IQ test - WICS (5-15); neuropsychological study of the functional development of neuropsychological components was conducted using complex neuropsychological diagnostics, which was based on the method of neuropsychological diagnostics of children by L.S. Tsvetkova, as well as additional diagnostic methods developed and adapted by the authors.

Using the Wechsler test, the general intellectual indicator was calculated, which, taking into account age characteristics, was correlated with the following scale: Mental defect; Borderline level; Reduced level; Average level; Good norm; High; Very high.

Using the neuropsychological technique, the functioning of the following neuropsychological components of mental activity was studied: energy factor; factor of control and programming of activity; inhibitory control; spatial factor; visual memory; auditory-verbal memory (inhibition of traces under interference conditions); representation of images; visual-object perception; phonemic hearing, perception of non-speech sounds; perception of rhythms; factor of interhemispheric interaction; kinetic factor; kinesthetic factor. Neuropsychological components are considered as a factor composition that correlates with the functional development or dysfunction of the cortical and subcortical structures of the brain.

The following tests were used to identify the functional state of the neuropsychological components of mental activity: 1) tests to study praxis (“fist-edge-palm”, “test of reciprocal hand coordination”, “transfer of poses according to a kinesthetic pattern from one hand to the other”, “Head's tests”, test of regulatory praxis - “Raising/not raising a hand according to a sound signal”, “Praxis of hand posture”, “Oral praxis”); 2) tests to study gnosis (“recognition of simple images”, ”recognition of noisy images”, “recognition of unfinished images”, “recognition of a complex plot picture”, “phonemic hearing”, “Perception of non-speech sounds”, “Perception of rhythms”, “Drawing with a 180-degree turn”); 3) tests to study auditory-verbal and visual memory (“two groups of three words”, “two sentences”, “10 words”, “6 difficult-to-verbalize pictures”; 4) speech research (“Binet tests”, “Inverted constructions”, “Planning a speech utterance”, “Phonemic perception”,); 5) tests to study thinking (“story based on a complex plot picture”, “composing a story based on a series of plot pictures”, “the fourth one is extra”, “Kos’s cubes”, “Synthesis of a picture from parts”); 6) tests to study attention, executive functions (“Test for asymmetry of visual attention”, “Composing a story plan”, “Proofreading test”, “Observation”); 7) methods for studying the energy component of activity (questionnaires for parents “Questionnaire of the functional state of the diencephalic and brainstem structures”, “Observation method”. Based on the test results, qualitative and quantitative analysis was carried out.

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Subjects. Subjects were selected based on similarity of socio-demographic and mental health indicators. The study involved children of a wide age range from 3 to 15 years. Each child participates in the project on the basis of informed voluntary consent signed by the parents.
Inclusion criteria for the ART group: conception of a child by ART (IVF, ICSI, IS); age from 3 to 15 years; children with different mental development from conditionally normal to neuropsychiatric disorders.

Inclusion criteria for the comparison control group: children conceived naturally; age from 3 to 15 years; mental development from conditionally normal to neuropsychiatric disorders.

Mothers of children in both groups have relative similarities in the course of pregnancy. ART group - a total of 110 children conceived with the help of assisted reproductive technologies were examined, including 62 boys, all aged from 3 to 15 years, the average age was 7.1±2.9 years, conceived with the help of IVF and ICSI; 12 pairs of twins (10 twins and 2 triplets). Comparison group (CG) - natural conception, 104 peers (56 boys), the average age was 7.0±3.1 years. Psychiatric diagnoses: about 25% of children with ART (diagnoses: schizotypal personality disorder; mixed behavioral and emotional disorder, ASD); in the group of children with ART - about 10% (ASD, ADHD). In the group of children with ART, difficulties during childbirth were noted in 70% of cases; in the group of children with natural conception, difficulties during childbirth were noted in 60% of cases. The majority (80%) of ART children worked with a speech therapist, neuropsychologist individually or with a speech therapist in kindergarten and school; in the group of children with natural conception - 55%. The study was approved by the Ethics Committee of the Scientific Center for Mental Health.

RESULTS

The article describes the results of a comparison of two groups (natural conception group - CG, and ART group). Data were analyzed in the following areas: 1) perinatal pathology, 2) psychometric intelligence test, 3) neuropsychological study.
1) Presence of pre- and perinatal pathology: gradation was carried out on a scale: severe perinatal pathology, mild perinatal pathology, absence of perinatal pathology. The results obtained are presented in Table 1.

Table 1

Pre- and perinatal pathology

Pre- and perinatal pathology	*severe pathology*	*mild degree*	*total*
CG group	35%	16%	51%
ART group	60%	10%	70%
	ϕ* emp = 3.578	ϕ emp = 1.266	ϕ*emp = 2.765

Table 1 shows that the frequency of severe perinatal pathology is significantly higher in the group of children receiving ART. Moreover, the percentage of children without any pre- or perinatal pathology (mild or severe) is significantly higher in the group of children in the CG.

To determine the significance of differences, Fisher's test was used.
2) Psychometric assessment of intelligence was carried out using the Wechsler test (WISC), different levels of intellectual development were identified (from mental defect to very high intelligence). The data are presented in Table 2.

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Table2

Percentage of occurrence by groups of levels of intellectual development

IQ	*ART*	*CG*	*Fisher criterion*
			ϕ 00,1=1,64; ϕ 00,5=2,31
Mental defect	4%	0%	
Border level	3%	1%	ϕ emp = 0.62
Reduced level	4%	4%	ϕ emp = 0.032
Average level	40%	28%	ϕ emp = 1.618
Good norm	24%	31%	ϕ emp = 1.11
High	14%	28%	ϕ emp = 2.214
Very tall	14%	9%	ϕ emp = 0.971

As a result, although there were no significant differences between the natural conception groups of the CG and ART in terms of different levels of intellectual development, in percentage terms there is a tendency towards a higher percentage of the occurrence of good norms and high intelligence in children from the group with natural conception. In addition, in the group of natural conception there are no children with intelligence at the level of mental defect.

3) Neuropsychological diagnostics (adapted version of the Luria-Tsvetkova technique) [20]. The following neuropsychological components were assessed: general neurodynamic (energy factor), visual memory, auditory-speech memory (inhibition of traces of auditory-speech memory), visual-object perception, phonemic hearing, activity planning (programming factor), inhibitory control (inhibition of the dominant reaction), visual-spatial and quasi-spatial perception, interhemispheric interaction, kinetic factor (inertial mobility of motor stereotypes), kinesthetic factor. Gradation for each of the neuropsychological components: pronounced functional immaturity\deficit; slight underdevelopment; development norm. In Table 3 shows the percentage of occurrence in the CG and ART groups of pronounced functional immaturity in terms of neuropsychological components of mental activity.

Table 3

Percentage of gross immaturity/deficiency of neuropsychological components

Neuropsychological components	ART % gross immaturity	CG % gross immaturity	Fisher criterion ϕ 00,5= 2,3 ϕ 00,1=1,64
Energy factor	56%	29%	ϕ* emp = 3.917
Visual memory	32%	15%	ϕ* emp = 2.885
Auditory-speech memory	65%	41%	ϕ* emp = 3.429
Visual-object perception	10%	2%	ϕ* emp = 2.546
Phonemic hearing	27%	32%	ϕ emp = 0.778
Programming Factor	36%	19%	ϕ* emp = 3.479
Inhibitory control	59%	36%	ϕ* emp = 3.288
Quasi-spatial perception	35%	23%	ϕ emp = 1.881
Visuospatial perception	26%	17%	ϕ emp = 1.556
Factor of interhemispheric interaction	43%	29%	ϕ emp = 2.072
Kinetic	57%	40%	ϕ* emp = 2.418
Kinesthetic	26%	12%	ϕ* emp = 2.567

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Table 3 shows that for most components the percentage of severe deficits is lower in the CG group. The only exceptions are phonemic hearing and visual-spatial perception. In our opinion, such specific development, on the one hand, indicates a tendency toward functional immaturity (a larger percentage of pronounced deficits) of the vast majority of factors in the group of ART children. This identifies the risks associated with neurocognitive development when using assisted reproductive technology procedures. On the other hand, a number of neuropsychological components have been identified, especially those related to speech functions (phonemic hearing, quasi-spatial perception), for which there are no or insignificant differences between the groups. In our opinion, this may indicate a certain potential for neurocognitive development in the group of ART children, which is revealed during directed training even in the case of a decrease in the main components of neurocognitive development. The greatest differences in the percentage of occurrence of severe immaturity were identified for the following components: energy factor, activity planning, inhibitory control.

Let's move on to comparing the percentage of representation of normative development in the compared groups (see Table 4).

Table 4

Percentage of occurrence of normative development of neuropsychological components

Neuropsychological components	*ART % normative development*	*CG % normative development*	*Fisher criterionφ 00,5= 2,3 φ 00,1=1,64*
Energy factor	12%	16%	ϕ emp = 0.82
Visual memory	42%	56%	ϕ emp = 1.987
Auditory-speech memory	13%	28%	ϕ* emp = 2.666
Visual-object perception	76%	91%	ϕ* emp = 2.927
Phonemic hearing	46%	50%	ϕ emp = 0.566
Programming Factor	30%	37%	ϕ emp = 1.054
Inhibitory control	20%	25%	ϕ emp = 0.849
Quasi-spatial perception	27%	42%	ϕ emp = 2.242
Visuospatial perception	26%	47%	ϕ* emp = 3.118
Factor of interhemispheric interaction	30%	41%	ϕ emp = 1.633
Kinetic	13%	22%	ϕ emp = 1.683
Kinesthetic	14%	55%	ϕ* emp = 6.392

Table 4 shows that under normal conditions, not burdened by perinatal pathology and/or other negative developmental factors, the percentage of occurrence of normative development in groups is almost the same (fewer significant differences). But the trend towards a higher percentage of normative development in the natural conception group (CG) still persists. The greatest differences were identified in the following components: kinesthetic factor, visual-spatial perception.

DISCUSSION

Obviously, the results obtained allow us to speak about a wide variety of developmental variants in IVF children, about the presence of perinatal pathology in a significant number of cases (about 70%), about the peculiarity of speech formation, similar to what other authors have seen in their works [18]. An unambiguous conclusion about the violation of speech development in children born by IVF cannot be made, but in the presence of mental pathology and taking into account the age of the mother and the number of ART procedures used, attention should be paid to the provision of speech therapy and neuropsychological correction with a speech therapist.

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The twin pairs of IVF children also showed diversity, but at the same time in a significant part of cases the developmental level and neuropsychological status of the children were similar, even in the presence of psychiatric pathology. Apparently, environmental components (formative education, timely correction, parents' attitude to the child's development) have a positive impact.

Of course, the specifics of the institution where IVF and CG children came for counseling should also be taken into account = expansion of samples, more detailed consideration of mental health problems, so additional research is required.
To summarize, let us try to formulate a possible answer to the questions about the pros and cons of ART.

"Pros" - a more attentive attitude to the period of pregnancy, always long-awaited and beloved child, more often well-to-do parents, improvement through a variety of additional activities that have a developmental and corrective orientation; ART is possibly associated with assistance (neuropsychological correction and additional activities and attention).

"Cons" - risk factors for worsening the development of a child conceived with the help of ART - polypregnancy and complications of pregnancy and childbirth (may be common with naturally conceived children). Age of the parents at the time of conception, number of implantations, everything related to the ART procedure - type of ART, use of cryoembryos, availability of donor eggs and sperm,

insufficient study of the nuances of ART and recommendations on the care and upbringing of the IVF child.
We analyzed both the disadvantages, "minuses" of the application, and possible options for their leveling through developmental and corrective modern technologies.

The development of medicine, humanization of society, the use of new reproductive technologies along with the problems of the negative impact of ecology and civilization on child development requires reflection in the context of psychological, medical, pedagogical and social support of modern children.

IVF children are always long-awaited and desired, parents make maximum efforts and opportunities, do all the best for their development and despite the fact that the use of IVF and other ART causes many religious, ethical, legal and psychological issues, according to the data of the World Health Organization (WHO).

According to the WHO, neither the physical health nor the mental development of children conceived by IVF (there are over 10 million such people in the world) is fundamentally different from those conceived naturally [5,10]. However, it should be noted that at the end of the 20th century and at the very beginning of the 21st century there were more works pointing to the negative consequences for the mental health and development of children of the use of ART at the stage of conception than first quarter of the 21st century.

ART at the stage of conception than we currently see. The question whether this is a consequence of the improvement, optimization of ART itself or is determined by some other reasons is still open [2, 13, 16, 19].

CONCLUSIONS

• The positive consequences of ART (besides the happiness of parenthood) include greater attention to the upbringing and education/training of the child.

• Conditional negative consequences of using ART – a significantly higher incidence of perinatal pathology compared to the group of natural conception; a significant deficit in the neurodynamic (energy) component of activity and a number of other neuropsychological factors is more present in the ART group than in the natural conception group.

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• In our opinion, further research is needed as significant differences have been found. It is necessary to search for the reasons for these differences, as well as diagnostic tools, causes of negative development and predictors of positive development.

• A more detailed neuropsychological study is also necessary in connection with the presence of perinatal pathology, neuropsychiatric diseases, including to determine the necessary assistance (parental assistance, psychological and pedagogical, therapeutic and speech therapy, assessment of the type of obstetric care, etc.).

• Assessment of intelligence using various types of diagnostics (not only Wechsler)

• Longitudinal follow-up in both groups.

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