УДК: 618.177-089.888.11
DOI: 10.37800/RM.1.2022.15-22

HEALTH STATUS OF CHILDREN BORN AFTER ASSISTED REPRODUCTIVE TECHNOLOGIES

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Annotation

Relevance: The health status of desired children born after the successful use of assisted reproductive technologies (ART) remains one of the most discussed in modern medicine. Existing publications on the use of ART, including extensive registry studies and systematic reviews/meta-analyses, have conflicting data regarding the health status of children conceived through in-vitro fertilization compared to those conceived naturally.

Most studies are mainly devoted to short-term observations of the state of somatic or mental childrens'/offspring health after ART, while publications concerning long-term results are much less common.

The study aimed to analyze modern publications on physical and sexual development features, psychosocial status, endocrine system status, risks of cardiometabolic diseases, and conformational abnormalities of children conceived using ART.

Methods: This review includes an analysis of the currently available data on the childrens'/offspring health born after ART. The literature was searched in online databases, including Medline, Scopus, Web of Science, Google Scholar, Springer, PubMed, ResearchGate, and CyberLeninka. The search was carried out on all types of studies published in English and Russian, using the keywords: "assisted reproductive technologies (ART)," "in vitro fertilization (IVF)," "offspring," "children," "childrens'/offspring health," "state of health," "psychosocial health."

Results: The literature data analysis revealed several studies on the possible impact of the state of health of their parents on the health of offspring in the cases when the parents decreased fertility is an indication for ART. Excluding such factors levels the probability of an adverse effect of ART on future children's health.

Conclusion: Considering the active development of ART in Kazakhstan, a large cohort of children born after ART, and the lack of studies on their morbidity's health status and structure, an active study of this problem in our country is required.

Keywords: *assisted reproductive technologies (ART), in vitro fertilization (IVF), offspring, children, the children's health, state of health, psychosocial health.*

Introduction: One in seven couples suffer from infertility, and many of these couples require assisted reproductive technology (ART) [1]. The use of ART has increased substantially in recent decades: more than 390 000 children are born each year worldwide, and the total number of children born after ART now exceeds 9 million [2]. If this trend continues and there is no further growth in infertility services, approximately 167 million people will owe their births to these technologies by 2100, representing about 1.4% of the world's population [3].

The development of modern reproduction in Kazakhstan has a relatively long history since the 50s of the 20th century. In October 1995, the first ART laboratory was opened in the country; on July 31, 1996, the first test-tube baby in Kazakhstan was born [4]. Today, the use of ART is rapidly developing, and advanced methods and technologies are actively introduced. More than 30 000 children have already been born after ART. However, the state of childrens'/offspring health born to infertility patients after successful use of ART and their further development remains the focus of attention of researchers and clinicians.

Most current reviews and publications on children's health after ART are found in foreign literature. A review of existing publications reveals contradictory results resulting in opposite approaches and attitudes towards ART.

The study aimed to analyze modern publications on physical and sexual development features, psychosocial status, endocrine system status, risks of cardiometabolic diseases, and conformational abnormalities of children conceived using ART.

Materials and methods: Literature searches were performed on online databases including Medline, Scopus, Web of Science, Google Scholar, Springer, PubMed, ResearchGate, and CyberLeninka. The search was carried out for all types of studies published in English and Russian, using the appropriate titles and keywords: "assisted reproductive technology (ART)," "in vitro fertilization (IVF)," "offspring," "children," "children's health," "state of health," "psychosocial health." The articles were checked for information on the health and development of offspring conceived by ART. Full-text articles were evaluated for eligibility. Inclusion criteria were established before the literature search. They included original case-control studies, cohort studies, meta-analyses, systematic reviews that reported perinatal and later health outcomes for offspring conceived by ART, and previous reviews on the topic. Studies were excluded if they presented grouped data on offspring conceived as a result of a specific IVF method, preventing the extraction of data on the general condition of children, as well as when the study focused on maternal outcomes, the course of pregnancy without taking into account data on the childrens'/offspring health. Further, the analysis of the data available to date on the general condition and features of the development of children born after ART was carried out.

Results: Most studies have found no differences in

anthropometric characteristics between children born from artificial insemination and children conceived naturally [5, 6]. At the same time, several publications revealed the differences in anthropometric measurements at different ages [7, 8].

L. Meddeb et al. [9] found the effect of ART on an increased risk of preterm birth and an increase in the birth of children with low body weight.

Some studies have also found a high incidence of conformational abnormalities and chromosomal abnormalities, intrauterine developmental delay, infantile cerebral palsy, infectious diseases, and prematurity in these children. However, other authors claim no nonconformities in the physical health and psycho-emotional development of children born after ART [10].

The likelihood of distant cardiovascular consequences and metabolic risks in children born through artificial insemination has attracted particular interest over the past decade and has conflicting data to date. According to U. Scherrer et al. [11], children and adolescents conceived by ART have marked vascular dysfunction of the systemic and pulmonary circulation. Apparently, this problem is not related to parental factors or hormonal stimulation of ovulation in the mother but to the ART procedure itself. B.C. Fauser et al. [12] found that children conceived with IVF have lower birth weight and more subcutaneous fat, higher blood pressure, and higher fasting glucose concentrations than children conceived naturally. In addition, it is known that insulin sensitivity is significantly lower in the group of children born after ART compared to naturally conceived children [13]. Some studies confirm that childhood cardiovascular and metabolic risk factors may worsen later in life and may eventually cause chronic cardiometabolic diseases. Considering small cohorts with a high risk of systematic selection error in most studies, E. Norrman et al. [2] concluded that children born after ART had no increased risk of cardiovascular disease or diabetes mellitus type II after adjustment for measured intervening factors. In contrast, there was a small but elevated risk for obesity. Consequently, cardiometabolic outcomes in children born after ART are generally encouraging. However, further studies with longer follow-ups are needed.

It is biologically possible that ART may cause childhood morbidity. One hypothesis is that mechanical and hormonal manipulation of gametes and the embryo induce epigenetic changes that can affect the immune system and reduce disease resistance. Intracytoplasmic sperm injection (ICSI) has been used in clinical practice since 1992, initially only for the treatment of male factor infertility. ICSI is often used in cases of mild male infertility, unexplained infertility, and failures during fertilization since it has proven to be an effective fertilization method, bypassing the natural selection of spermatozoa. The proportion of ART procedures involving ICSI has increased worldwide from 47.6% in 2000 to 66% in 2010 and exceeds 90% in some countries. With this increased use, it is critical to understand any potential adverse effects on offspring conceived by ICSI [14].

However, most studies show a weak association between ART and childhood morbidity, indicating the possibility that the real underlying cause of morbidity in these children may not be the ART treatment itself but other factors associated with inclusion in the treatment program, i.e., reduced fertility. D. Kuiper et al. (15) reported that children of subfertile couples are at increased risk for adverse perinatal outcomes and congenital disabilities compared to naturally conceived children of fertile couples, even if parents have not received fertility treatment. Another potential explanation for the increased morbidity observed in children conceived through ART could be differences in parental behavior between children conceived through ART and those conceived spontaneously (16). In a review by E.G. Pitskhelauri [17], some authors reported a 30-40% higher risk of congenital anomalies in children born through IVF. This index reached 25% in children born to parents with a history of infertility who refused an IVF procedure [17].

In the Upstate KIDS study, exposure to high levels of androgens in the womb with a history of polycystic ovarian syndrome (PCOS) increased the risk of obesity and child development, especially in girls [18]. This conclusion was confirmed by several extensive studies in Europe using data that found an association between maternal PCOS and/or increased fetal testosterone levels and an increased risk of autism, attention deficit hyperactivity disorder (ADHD), and pervasive developmental disorders [19, 20].

In women with gynecological pathology such as endometriosis receiving ART, the frequency of fertilization decreases which may be caused by excessive local production of proinflammatory cytokines, including interleukins and tumor necrosis factor-alpha (TNF-α) [21]. According to the inflammation hypothesis, women with endometriosis are at increased risk of hypertension and cardiovascular disease, indicating long-term health consequences of inflammation beyond reproductive age [22]. Uterine myoma occurs in 70% of women and is also associated with infertility [23]. Some suggest that inflammation may also play a role in the pathogenesis of uterine fibroids, and women with fibroids appear to be at higher cardiovascular risk [24]. Since inflammation is associated with adverse pregnancy and child health consequences, future epidemiological studies should assess the long-term health effects of children conceived by ART by mothers with uterine fibroids and endometriosis [25].

Male and female obesity increases the risk of infertility. In women, obesity is associated with anovulation, miscarriage, and prolonged pregnancy. First of all, it is assumed that the effect of obesity is associated with hormonal disorders since adipose tissue is an active metabolic and endocrine organ. An increase in DNA fragmentation and epigenetic effects in men is being actively studied today [25]. According to P. Suren et al., a study of a large cohort of newborns from Norway demonstrated a stronger linear relationship between paternal body mass index (BMI) rather than maternal BMI and the risk of developing autism [26].

A known association between hypothyroidism, ovarian dysfunction, and menstrual cycle disorders can decrease fertility and indicates infertility treatment. It is important to note that overt hypothyroidism is positively associated with infertility, while subclinical hypothyroidism is not, although there are discussions about the appropriate thresholds for their differentiation. Undetected or inadequately treated obvious maternal hypothyroidism leads to cognitive impairment in the offspring, even in the absence of neonatal hypothyroidism. Subclinical hypothyroidism, defined as a high level of thyroid-

stimulating hormone (TSH) with thyroxine (T4) within the normal range for gestational age, is associated with a decrease in IQ in children. However, to date, there is no evidence that the combined effects of hypothyroidism, infertility and ART can impact the health of offspring [25].

Over the past few decades, the rates of delayed childbearing have increased, as a result of which the age of the mother has increased. The mother's age≥35 years increases the risk of complications in pregnant women and newborns and may also increase the risk of chromosomal abnormalities. Based on an increase in the frequency of preterm birth and other adverse neonatal outcomes, a higher risk of adverse long-term outcomes can be expected. The father's age may also play a role that is sometimes difficult to separate from the influence of the mother's age because pairs tend to be correlated by age. For example, the International Pediatric Leukemia Consortium identified an increased risk of acute lymphoblastic leukemia associated with older paternal age, with mixed results for older maternal age because of collinearity of age information. However, the accumulated data suggest that the father's age and paternal risk factors, in general, may be necessary for the assessment [25].

Various explanations have been proposed for why children conceived by ART may experience more psychosocial health problems than children conceived naturally. Firstly, the use of ART is associated with an increased risk of adverse birth outcomes, such as low birth weight and prematurity, which can lead to negative consequences. Secondly, compared to natural conception, conception using ART may be associated with a higher level of parental stress, affecting the relationship between parents and children and the psychosocial development of children. Scientists claim that a child born after ART can be treated specially, with excessive protection from parents or inflated expectations [27]. However, several studies have shown that children under the age of seven born after ART have better cognitive skills than children conceived naturally and have suggested that these differences are mainly due to the favorable socioeconomic characteristics of couples who have access to fertility treatment [28, 29]. S. Sandin et al. [30] studied more than 2.5 million children born in Sweden from 1982 to 2007 and found that mental retardation risk was significantly higher in children conceived through ART than their counterparts from natural pregnancies. A recent systematic review on cognitive development after ART [31] found that IVF methods negatively impact cognitive development [30, 32, 33]. A Danish registration study reported a comparable risk of mental retardation in children from a single pregnancy through ART and spontaneously conceived [34]. Recent extensive registry-based studies in Sweden and Denmark have shown similar schooling rates for children after IVF and children born by spontaneous conception [35-48]. C. Fountain et al. [39] studied 6 million live births and found that autism was twice more common in children conceived by ART than after natural pregnancies. However, most neurocognitive development and autism spectrum disorders studies do not prove an increased risk when adjusted for multiple births [40]. While studies of parent-child relationships and children's psychosocial health have yielded mixed results, most reported similar results in both groups. There is some evidence that having a child with older parents positively affects parenting because these parents demonstrate higher levels of emotional involvement, lower levels of stress, and a greater sense of competence (41, 42). The European Study of families with ART results has shown that positive relationships between mothers and children are a feature of ART throughout childhood and adolescence [43]. In general, the existing evidence on the long-term psychosocial health of ART children is inconclusive, as several studies that have looked at the outcomes of these children after childhood have had mixed results [44, 45]. As for academic performance, according to numerous studies, children born after ART do not differ from their peers conceived naturally [46-48].

Discussion: Thus, an analysis of the literature on the health status of children born after IVF has revealed inconsistencies in the results obtained which requires further study. In order to improve the reliability of the information on the health of offspring born as a result of IVF, it is necessary to take into account the anamnesis of the parents entering the IVF program since the causes of infertility themselves may serve as the basis for the development of pathological conditions in the children born.

Conclusion: The increase in the frequency of infertility and its successful correction using ART in recent decades has led to an increase in the number of children conceived through artificial insemination and increased questions about the potential risks to their health. The available scientific evidence on the state of the offspring health is contradictory and requires further study. Despite the active, practical use of ART in Kazakhstan, there was no study of morbidity structure and health status of children conceived by ART to allow the development of a prognostic model and general principles of their management. Currently, in countries such as Denmark [49], Japan [50], Switzerland [51], and others, there are national registries of data on assisted reproductive medicine, which makes it possible to extract recommendations for improving current practice, preventing complications associated with ART and amend the current legislation relating to this field of medicine. The introduction of a national register in Kazakhstan will allow complete recording of all ART information from public and private clinics, monitoring and research on the treatment of infertility and reproductive function in women seeking ART, and monitoring the health status of children born after ART. A national registry can become a valuable research tool and a key component of Kazakhstan's Health Information System for Human Reproduction.

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ОСОБЕННОСТИ СОСТОЯНИЯ ЗДОРОВЬЯ ДЕТЕЙ, РОДИВШИХСЯ С ПОМОЩЬЮ ВСПОМОГАТЕЛЬНЫХ РЕПРОДУКТИВНЫХ ТЕХНОЛОГИЙ

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Аннотация

Актуальность: Проблема, связанная с состоянием здоровья желанных детей, родившихся после успешного применения вспомогательных репродуктивных технологий (ВРТ), остается одной из наиболее обсуждаемых в современной медицине. Существующие публикации о результатах применения ВРТ, включая крупные регистрационные исследования и систематические обзоры/мета-анализы, имеют противоречивые данные в отношении состояния здоровья детей, зачатых в результате оплодотворения in vitro, по сравнению с детьми, зачатыми естественным путем.

Большинство исследований посвящены в основном краткосрочным наблюдениям за состоянием соматического или психического здоровья детей после ВРТ, в то время как публикации, касающаяся долгосрочных результатов, встречаются гораздо реже.

Цель исследования – анализ современных публикаций об особенностях физического и полового развития, психосоциального статуса, состояния эндокринной системы, рисков развития кардиометаболических заболеваний и врожденных пороков развития детей, зачатых с помощью ВРТ.

Методы: Данный обзор включает анализ имеющихся на сегодняшний день данных о здоровье детей, родившихся в результате применения методов ВРТ. Поиск литературы был осуществлен в онлайн-базах данных, включая Medline, Scopus, Web of Science, Google Scholar, Springer, PubMed, ResearchGate и Cyberleninka. Поиск проводился по всем типам исследований, опубликованных на английском и русском языках, по ключевым словам: «вспомогательные репродуктивные технологии (ВРТ)», «экстракорпоральное оплодотворение (ЭКО)», «потомство», «дети», «здоровье детей/потомства», «состояние здоровья», «психосоциальное здоровье».

Результаты: На основе анализа данных литературы сделан вывод о том, что в ряде исследований были упущены данные о возможном влиянии на состояние здоровья потомства состояния здоровья их родителей, приведшего к снижению фертильности и ставшего показанием для проведения программы ВРТ. При исключении данных факторов вероятность неблагоприятного влияния самой процедуры ВРТ на показатели здоровья будущих детей, как правило, нивелируется.

Заключение: Учитывая активное развитие ВРТ в Казахстане, наличие достаточно большой когорты детей, родившихся в результате применения ВРТ, и отсутствие работ по изучению состояния здоровья и структуры их заболеваемости, требуется активное изучение данной проблемы в нашей стране.

Ключевые слова: *вспомогательные репродуктивные технологии (ВРТ), экстракорпоральное оплодотворение (ЭКО), потомство, дети, здоровье детей/потомства, состояние здоровья, психосоциальное здоровье.*

КӨМЕКШІ РЕПРОДУКТИВТІ ТЕХНОЛОГИЯЛАРДЫҢ КӨМЕГІМЕН ТУЫЛҒАН БАЛАЛАРДЫҢ ДЕНСАУЛЫҚ ЖАҒДАЙЫНЫҢ ЕРЕКШЕЛІКТЕРІ

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Аңдатпа

Өзектілігі: Қосалқы репродуктивтік технологияларды (ҚРТ) табысты қолданғаннан кейін туған қалаулы балалардың денсаулық жағдайына байланысты мәселе қазіргі медицинада неғұрлым талқыланатын мәселелердің бірі болып қалуда. ҚРТ қолдану нәтижелері туралы қолда бар жарияланымдар, оның ішінде ірі тіркеу зерттеулері және жүйелі шолулар/метаталдаулар табиғи жолмен туылған балалармен салыстырғанда invitro ұрықтандыру нәтижесінде пайда болған балалардың денсаулық жағдайына қатысты қарама-қайшы мәліметтерге ие.

Зерттеулердің көпшілігі негізінен ҚРТ-дан кейінгі балалардың соматикалық немесе психикалық денсаулығының жай-күйін қысқа мерзімді бақылауға арналған, ал ұзақ мерзімді нәтижелерге қатысты жарияланымдар аз кездеседі.

Зерттеудің мақсаты – ҚРТ көмегімен туылған балалардың дене және жыныстық даму ерекшеліктері, психоәлеуметтік мәртебесі, эндокриндік жүйенің жай-күйі, кардиометаболикалық аурулардың даму тәуекелдері және туа біткен даму ақаулары туралы қазіргі заманғы жарияланымдарды талдау.

Әдістер: Бұл шолу ҚРТ әдістерін қолдану нәтижесінде туылған балалардың денсаулығы туралы қазіргі кездегі деректерді талдауды қамтиды. Әдебиеттерді іздеу Medline, Scopus, Web of Science, Google Scholar, Springer, PubMed, ResearchGate және CyberLeninka сияқты онлайн-дерекқорларда жүзеге асырылды. Іздеу ағылшын және орыс тілдерінде жарияланған зерттеулердің барлық түрлері бойынша, «қосалқы репродуктивтік технологиялар (ҚРТ)», «экстракорпоралдық ұрықтандыру (ЭКҰ)», «ұрпақтар», «балалар», «балалардың/ұрпақтардың денсаулығы», «денсаулық жағдайы», «психоәлеуметтік денсаулық» кілт сөздері бойынша жүргізілді.

Нәтижелері: Әдебиеттер деректерін талдау негізінде бірқатар зерттеулерде ұрпақтардың денсаулық жағдайына, олардың ата-аналарының денсаулығына әсер етуі мүмкіндіктері туралы мәліметтер жоқ, бұл ұрықтылықтың төмендеуіне әкеліп соқтырды және ҚРТ бағдарламасының көрсеткіші болды деген қорытынды жасалды. Осы факторларды алып тастағанда, ҚРТ рәсімінің өзі болашақ балалардың денсаулық көрсеткіштеріне қолайсыз әсер ету ықтималдығы, әдетте, жойылады.

Қортынды: Қазақстанда ҚРТ-ның белсенді дамуын, ҚРТ қолдану нәтижесінде туылған балалар когортының жеткілікті үлкен болуын және денсаулық жағдайы мен олардың аурушаңдығының құрылымын зерттеу бойынша жұмыстардың болмауын ескере отырып, бұл мәселені біздің елімізде белсенді зерделеу талап етіледі.

Кілт сөздер: *қосалқы репродуктивтік технологиялар (ҚРТ), экстракорпоралдық ұрықтандыру (ЭКҰ), ұрпақтар, балалар, балалардың/ұрпақтардың денсаулығы, денсаулық жағдайы, психоәлеуметтік денсаулық.*

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Financing: Authors declare no financing.
Conflict of interests: Authors declare no conflict of interest.