

Features of perinatal outcomes in women after supporting reproductive technologies

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Abstract: *Pregnancy conceived with assisted reproductive technologies (ART) has a higher risk of maternal and perinatal complications, and the overall risk of adverse outcomes requiring extended obstetric care has not been thoroughly studied. The review is devoted to the actual problem of the health status of children born after IVF. A systematic review of the health indicators of children conceived with IVF after the neonatal period was carried out versus natural, conceived.*

Key words: *infertility, pregnancy, assisted reproductive technology, IVF.*

1. Introduction

Currently about 15% of married couples suffer from infertility. Assisted reproductive technologies (ART) are now widely used around the world due to the growing prevalence of infertility, as well as due to increased access to treatment and government funding for this method. Consequently, the number of children conceived after in vitro fertilization (IVF) is growing steadily every year [1, 11, 15].

This review presents the literature on perinatal outcomes in infants born after ART, including in vitro fertilization (IVF), intracytoplasmic sperm injection (ICSI), freezing, and more modern methods such as blastocyst culture and vitrification. The review is based on recent systematic reviews (SR) and large cohort studies. For rare outcomes, studies from PubMed, Medline / CyberLink, Web of Science, and Library.ru were included. A search was conducted for studies reporting the outcome of healthy infants conceived with IVF and ICSI.

Infertility, as a state problem and ways to solve it.

The rate of increase in infertile marriages and pre-conception of married couples using innovative technologies of in vitro fertilization (IVF), this method that has led to an increase in the number of pregnancies and has determined the study of relevance in the field of health and development of children. In the structure of modern stages of development of medicine, one of the most effective ways to solve problems among infertile married couples is in vitro fertilization, which is the only method of having children [3, 4, 6].

Today, one of the most important medical, social and national problems is infertile marriage. In many countries of the world, the frequency of infertile marriages tends to increase and is more than 15%. These indicators in Uzbekistan range from 8 to 17%, in Europe - about 10%, in the USA - 8-15%, in Canada - 17%, in Iran - 8%, in Kazakhstan - up to 15% [7]. In the Republic of Uzbekistan, despite the high natural population growth, the problem of infertility remains an urgent problem associated with the high frequency of somatic and gynecological pathologies among women of reproductive age. After that, an order was signed in the Republic of Uzbekistan regulating the procedure for the implementation of assisted reproductive technologies (reg. No. 3217 of February 6, 2020).

These days more than 8 million babies have been conceived after ART globally, and up to 6% (ranges from 0.2% to 6.4%) in European studies, newborns' have been conceived with

ART. ART includes standard in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) [5, 40].

Concerns remain about the potential health consequences of ART. More and more data show that ART treatment is associated with unfavorable perinatal outcomes, which are associated with decreased fertility of patients, multiple pregnancies and ART technologies [3, 17, 20]. According to international studies, children born with the help of new reproductive technologies are more often registered developmental anomalies [10, 14, 18, 19]. Thus, in his speeches, academician A. A. Baranov focuses on the fact that children born with the help of in vitro fertilization (75% of them have certain health disorders) differ sharply from their naturally conceived peers [1]. Wherein most scientific works are devoted to the study of the health status of children with high risk, specifically those born from multiple pregnancies after IVF [13, 15, 17, 22]. It is the multiple pregnancy as a result of IVF that is the risk of stillbirth and neonatal death of the child, the development of perinatal complications, somatic pathology, disorders of physical and neuropsychic development (NPD), the formation of congenital malformations (CM) and disability [4, 6, 8, 10]. At the same time, the results of major foreign epidemiological studies and meta-analyses have shown that children from singleton pregnancy after IVF also tend to be born prematurely, with low weight and a high incidence of neonatal diseases [27, 29].

IVF AND ICSI.

ICSI is a more advanced method in which a single sperm cell is injected into the oocyte's cytoplasm. ICSI was originally used to treat severe male factor infertility, but it is now also used to treat mild male factor infertility, mixed infertility, unexplained infertility and failed fertilization attempts [21, 27, 31]. Globally, there is an increase in the use of ICSI: 71.3% of new IVF / ICSI cycles were performed in Europe in 2014, as shown in the latest reports of the European Society for Human Reproduction and Embryology (ESHRE) [32]. Among fresh IVF cycles in the United States, the use of ICSI increased from 36.4% in 1996 to 76.2% in 2012, with the largest relative increase among cycles without male infertility [33].

Later, cryopreservation (freezing and thawing of embryos) gained popularity. In Europe, cryopreservation accounted for 27.4% of all cycles in 2014, the highest in Switzerland - 41.1%. Selective freezing of all good quality embryos and transfer in subsequent cycles, i.e., selective frozen embryo transfer (SFET), has recently been introduced as a way to reduce ovarian hyperstimulation syndrome and improve reproductive outcome [6, 34, 35].

The risk of developing of the disease.

While most deliveries after ART are uncomplicated, ART is associated with potentially adverse obstetric outcomes for both mothers and infants, including hypertensive disorders during pregnancy, preterm birth and low birth weight [2, 18, 36]. ART has also been associated with an increased risk of birth defects. Many of these adverse outcomes may be associated with higher rates of multiple pregnancies after ART [30, 33]. With the increased use of single embryo transfer, the rate of multiple pregnancies has dropped significantly, but is still unacceptably high in many countries. In 2014, ESHRE reported a 17.5% birth rate among ART recipients in Europe (from 4.3% to 30.6%) [38]. In 2016, in the United States, 31.5% of infants conceived with ART were born after multiple pregnancies, compared with 3.4% of all infants in the general population [39]. However, most data also show that single children receiving ART have more poor perinatal outcome compared to single births after spontaneous conception, for example, higher rates of preterm birth and low birth weight [31]. New ART technologies are constantly being introduced, and it is important to monitor the safety of ART and the health of ART offspring [40].

Perinatal outcomes.

It should be noted that many factors affect the perinatal outcomes of pregnancy resulting from the use of ART. Firstly, the average age of married couples participating in ART programs is 34-35 years, as a result of which the chances of genetic disorders in the unborn child and pregnancy complications are increased. Secondly, infertility is most often associated with medical and genetic problems of parents, which can affect the health of the next generation. Third, medications received by women before and after artificial insemination can cause changes in the growing embryo [32]. Many authors pay attention to the fact that human manipulation with oocytes and spermatozoa, drug therapy of infertility, embryo transfer can be potentially dangerous for a growing fetus [5, 8, 37].

According to Ericson and co-authorship, there was a threefold increased risk of neural tube defects, gastrointestinal atresia and omphalocele in children conceived with ART. The authors note an increased risk of hypospadias in children after using the method of intracytoplasmic sperm injection into the cytoplasmic oocyte (ICSI). According to a study by Tararbit and co-authors [38], there is an increase in the frequency of heart defects in children conceived using ART. The authors found a significantly increased risk of malformations by outflow and ventriculoarterial connections of the heart, anomalies of the cardiac neural crest and double divergence of the great vessels from the right ventricle [5, 7, 38].

According to research by O.A. Kraev and co-authors [14], this study compared the health status of 34 children conceived after in vitro fertilization and 37 children conceived naturally. A study was conducted of the anamnesis of mothers, the health status of children from the neonatal period to 1 year. Thus, children from induced pregnancy in the neonatal period are more likely to suffer infectious diseases. In children under 1 year of age, hydrocephalus of the subcompensated form is more often formed, as well as a delay in the development of rates, which determines the III and IV health groups [14, 27, 35].

According to the dissertation work of N.A. Maslyanyuk, full-term infants from multiple pregnancies after IVF, intrauterine infection and perinatal hypoxic damage to the central nervous system predominate in the structure of perinatal pathology, which, in combination with fetal growth restriction syndrome, determines a high frequency (every second child) of symptoms of neuro-reflex excitability and suppression in the function of the central nervous system (CNS) and 38% of children - dysfunctions of the gastrointestinal tract [11].

When assessing the health status of children after IVF, according to B.C. Kuznetsova, a high frequency of hypoxic conditions (83.8%), perinatal pathology associated with the central nervous system (76.6%), intrauterine infection (58.6%), fetal growth retardation syndrome (FGRS) (30.5–65.7%), various fetal anomalies (34.8%). In addition, the prevalence of various fetal anomalies (1.4%) does not differ from similar indicators among the population. Among the morbidity in these children at an early age prevail diseases of the respiratory system (80.6%), digestion (51.1%), skin and subcutaneous tissue (49.2%), blood disease (35.0%), lag of physical development predominant until the first year of life [10]

In most studies, there was not observed difference in height between IVF conceived children and naturally conceived children. For example, considering recent US research, they have been compared 969 singletons, born as a result of fertility treatments, including ART and ovulation induction with or without intrauterine insemination, with 2471 singletons born naturally, and found that the growth and development of children under 3 years of age were comparable [33].

Infants born after slow frozen embryo transfer are known to have significantly higher birth weights than babies born after fresh embryo transfer [21, 33]. Similar data have been obtained for frozen embryo transfer using an open vitrification system. However, there are few data available regarding the birth weight using a complete closed embryo vitrification system. Two recent SRs, including singletons born after freezing oocytes as a result of slow freezing vitrification, found no difference in the risk of birth defects between freezing oocytes

and fresh cycles [26, 37]. One central Belgian study found that the frequency of any serious birth defects in single children, born after vitrification (n = 827) was similar after new cycles (n = 1374) [22, 31].

Maris E. I and coauthors [25] conducted a monocentric retrospective study, 371 babies were released as a result of fresh embryo replacement and 127 as a result of vitrified embryo transfer. The average birth weight of children was 205 g higher for frozen embryos compared to fresh embryo transfer groups (3368 g vs. 3163 g, respectively, $P < 0.001$). This difference persisted after multivariate analysis adjusted for additional factors such as gestational age, maternal age, mother's body mass index (BMI), exposure to tobacco, number of embryos transferred, and birth order ($P < 0.001$ [25, 26].

Placental development.

The placenta plays an important role in fetal development, transporting nutrients and oxygen, morphologically and functionally adapting to adverse environmental stresses and minimizing their effects on the fetus [28, 40]. Placenta's size can predict cardiovascular disease and insulin resistance. ART may also disrupt placental development and its function and, consequently, fetal growth in the womb [36, 38]. Increased placental thickness and placental hematomas have been reported, as well as pathological findings in pregnancies after ART [37]. IVF disrupts nutrient substances transfer through the placenta and metabolism in mice [28]. The weight of the placenta and the ratio of the weight of the placenta to the fetus with ART was significantly higher than with natural conception in humans and mice [21, 37, 39]. This was associated with a decrease in methylation levels and changes of genomic imprinting and expression of developmental genes in the treatment of ART in the placenta in mice and humans [33, 34]. Incorrect adaptive response of the placenta during This pregnancy can lead to adverse outcomes such as abortion, preeclampsia, or intrauterine growth restriction [35]. Although successful placental adaptation leads to normal pregnancy, the memory of epigenetic adaptation mechanisms established during pregnancy increases the risk of metabolic diseases later in life stage [36, 37, 38].

2. Conclusion.

The conclusions of numerous studies are that ART is a safe and effective treatment for infertility. In addition, perinatal outcomes have been improved over time. The increased use of single embryo transfer (SET), which avoids multiple pregnancies, is a major driver of improved outcomes observed in recent years. Several studies have shown that the perinatal outcome is better with a single use of ART compared with repeated use of ART, including twins [37, 39]. However, there is a moderately increased risk of adverse perinatal outcomes, including birth defects, in patients who received ART, compared to the general population overall. It is unclear if this is due to patient characteristics related to infertility or to the ART technique. Children receiving ART were mainly compared with children in the general population born after spontaneous conception. Patients with infertility may be older and more likely to have pre-existing comorbidities that may predispose to poor perinatal outcomes.

3. Literature

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