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THE INCIDENCE OF CONGENITAL MALFORMATIONS IN CHILDREN BORN IN CONSEQUENCE OF ASSISTED REPRODUCTIVE TECHNOLOGIES TAKING INTO ACCOUNT MEDICAL HISTORY

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Abstract

Assisted reproductive technologies (ART) become more and more popular. **The objective:** to determine the frequency and structure of congenital malformations in children born as a result of application of ART (ICSI) with taking into consideration anamnestic factors. **Materials and methods:** 74 children born after ART (ICSI) aged 1 month - 7 y. o. were examined. The presence of CM is confirmed by the data of laboratory and instrumental investigations. Along with clinical examination of the children the analysis of the antenatal and perinatal period was carried out, particular attention was paid to the study of the preconceptual stage peculiarities. **The results and discussion:** In the structure of CM those of cardiovascular system predominated with the share of (72.2 ± 10.5)%. Ventricular septal defect was diagnosed in (4. 1±2. 3)% in the group of the children under examination and this exceeds the general population figures. The combination of cardiac defects with other anomalies was observed in (16.7 ± 8, 8)% of children. CM of the digestive system were mainly represented by small anomalies of development and were diagnosed in (13. 5 ± 3. 9)% of the children. CM of the urinary tract was detected in (5. 4 ± 2.6) % of the examined children. Congenital defects of the musculoskeletal system were detected in (8. 1 ± 3. 2)% of the children. Congenital defects of the CNS were diagnosed in (4, 1±2, 3)% of the children.

The influence of various factors on the emergence of defects and anomalies of development was analyzed. CM's emergence was significantly influenced by mother's age ($\chi 2 = 4.18$, $p = 0.04$). The association of CMs emergence with anemia during the pregnancy was revealed ($\chi 2 = 5, 89$, $p = 0, 01$) also. **Conclusions:** In ART children congenital defects and malformations anomalies of the cardiovascular, urinary, digestive, musculoskeletal and sensory organs were the most frequent. The incidence of anomalies is associated with a state of somatic and reproductive health of the mother.

Key words: assisted reproductive technology, congenital defect and malformation.

Assisted reproductive technologies (ART) are becoming increasingly popular. Infertile married couples are turning for help to the specialized clinic of ART for treatment more often, while not every attempt is a success due to many factors: the somatic and reproductive health of parents, lifestyle, addictions, psychosocial factors, as well as drug load preparations containing higher doses of human hormones. According to ART clinics statistics, pregnancy occurs on average in 35-40% of cases, at that various methods of treatment are used, and not rare in the same patients because of virtue of previous therapy inefficiency. All of these factors can not pass without touching the health of the mother, fetus and further development and health of the child. This assumption is confirmed by numerous studies showing a high incidence of congenital malformations (CMF).

By the data of P. Sala et al. in 13 pregnancies (225 children) born after the use of intracytoplasmic sperm injection (ICSI) significant congenital anomalies (5.8%) were identified. Among them cerebral malformations were detected in 38.5%, abnormal limb development in 23.1%, while after natural conception these abnormalities were marked in 2.7% of 5.884 children. Thus, the children after ICSI or in vitro fertilization (IVF) are at twice the risk of developing congenital anomalies and chromosomal and musculoskeletal defects than babies born after natural conception [1].

Welmerink D. B et al. in their study compared the group of children born after ART and conceived in a natural way, with congenital malformations occurred in 6.2% patients in the control group (5.7%), while discernible pathology of the placenta from the mother received treatment in ART clinic (2.0%) against (0.9%) RR = 3.0 (2.0-4.7) [2].

Wennerholm U. B. et al. published Swedish results of determining the frequency of congenital anomalies in children born after ICSI. 1139 infants were examined, among them 736 *were born one,* 200 pairs of twins and one triple. In general there were 87 (7.6%) babies

with congenital anomalies. It is suggested that high levels of congenital anomalies, most likely is the result of a large number of multiple pregnancies after ICSI [3].

Pelkonen S. et al. estimated ART results under the condition of freezing-thawing and replanting, embryotransfering without cryopreservation, and those in the control group. In the first group congenital malformations constituted 4.2% of cases, in the second group 4.5% and 3.2% in the control group [4].

A high incidence of congenital malformations of this contingent of children need for further research on the structure of congenital anomalies and investigate the role of adverse medical history factors in their development.

The aim of our study:to determine the frequency and structure of congenital malformations in children born as a result of ART (ICSI), taking into account medical history factors.

Materials and Methods: To achieve the objectives of the study were examined 74 children born as a result of ART (ICSI), aged 1 month - 7 y. o. The congenital malformations were confirmed by laboratory and instrumental investigations. In addition to the clinical examination, antenatal and perinatal period of the children under study were analyzed, and special attention was paid to the study of the features preconceptional stage.

The results were processed with parametric and nonparametric methods with calculating the arithmetic mean, standard deviation. For the comparison of two mean values t-test (t) was used, the difference of compared parameters were considered statistically significant at $p < 0.05$. We analyzed the odds ratio for the study of communication events (OR) with 95% confidence interval, $\chi 2$ test. Statistical processing of the materials was carried out with the use of «EXCEL for Windows» software package, «STATISTICA 7.0 for Windows».

Results and Discussion:

In the structure of congenital anomalies malformations of the cardiovascular system with the share of 7.2 ± 10.5 % prevailed. Ventricular septal defect was detected in 3 children or 4.1 ± 2.3 % and exceeded the general population figures. Early detection of this defect at intrauterine growth was registered at 66.6 ± 27.1 % of children. The dimensions of the defect detected were 1.1 - 2.5 mm. Congenital heart disease - atrial septal defect (more than 2 - 3 mm) was detected in 10 (13,5 ± 3,9)% of the children surveyed.

Prenatal registration of malformation was not documented because the oval window is a physiological shunt at intrauterine growth. Patent ductus arteriosus was diagnosed in 4 (5.4 ± 2.6)% of children. One child (a girl) had an isolated anomaly - the membrane of the left

atrium separating the atrial cavity at apicoposterior and anteroinferior camera. Anatomical abnormalities in the structure of the heart which did not cause significant clinical and hemodynamic disturbances - small anomalies of heart development, such as left ventricular additional trabecular and valve prolapse were identified in 15 (20.3 ± 4.6)% of the children. The combination of cardiac malformations with other developmental abnormalities was observed in (16.7 ± 8.8)% of the children under examination. Cardiovascular system malformations were observed more frequently in girls (p> 0.05).

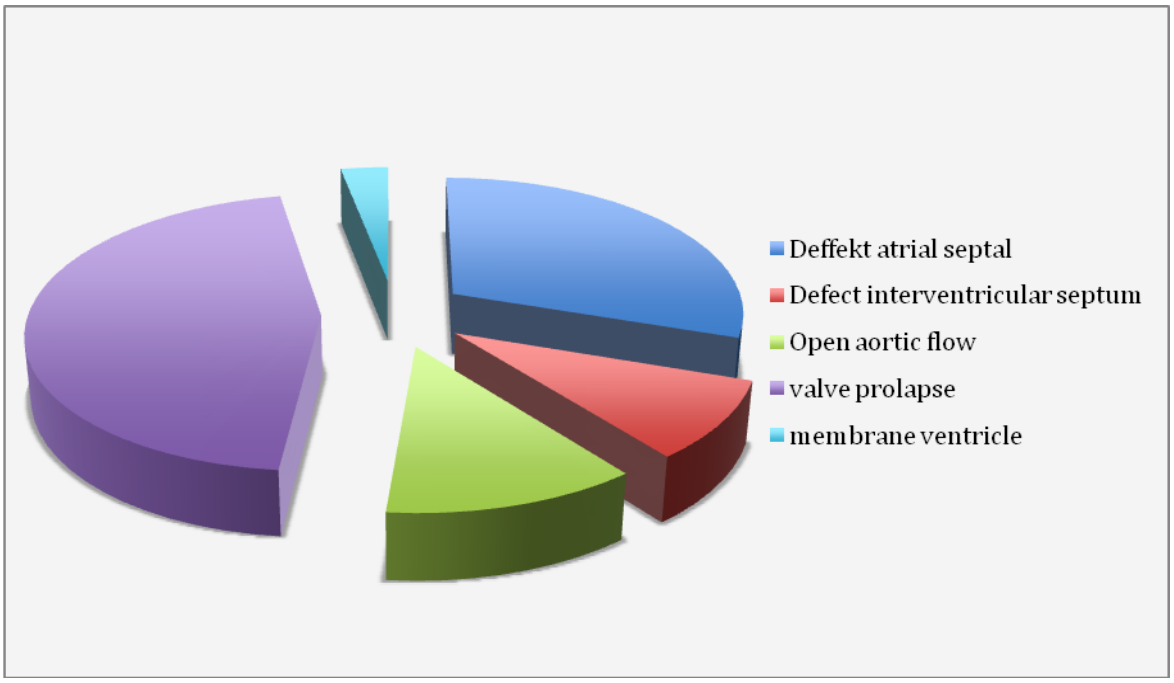

Fig. 1. Structure of cardiovascular system congenital malformations in the children under examination

Congenital malformations of the digestive system were mainly represented by small developmental anomalies. Biliary tract malformations were revealed at (13.5 ± 3.9)% of children and were not accompanied by functional disorders or were compensated. Usually they were diagnosed at the age over 3 years old. Anomalies of the gallbladder were more frequent in girls (p> 0.05). Incompetence of esophageal cardia with hypoplasia of the neuromuscular system of the lower esophageal sphincter was registered in one child in the early neonatal period.

Congenital malformations of the urinary system were detected in 4 (5.4 ± 2.6)% of the children under observation. According to the data of literature renal abnormalities are more common in girls, and the vices of urinary structures – in boys [5]. These results obtained

are in consistence with the pattern described. Quantitative abnormalities - doubling of the kidneys - were diagnosed in 2 girls, that constituted (2.7 ± 1.9)%.

The diagnosis of kidney malformations was carried out on the basis of antenatal fetal ultrasound data with the information about the increase of one of the kidney and expansion of the renal pelvis complex. In most cases there were cases of kidney disease in the family. The combination of malformations of the urinary system with other developmental anomalies was detected in one child. Cryptorchidism was diagnosed in (2.7 ± 1.9)% of the children under examination, with both abdominal and inguinal abnormalities.

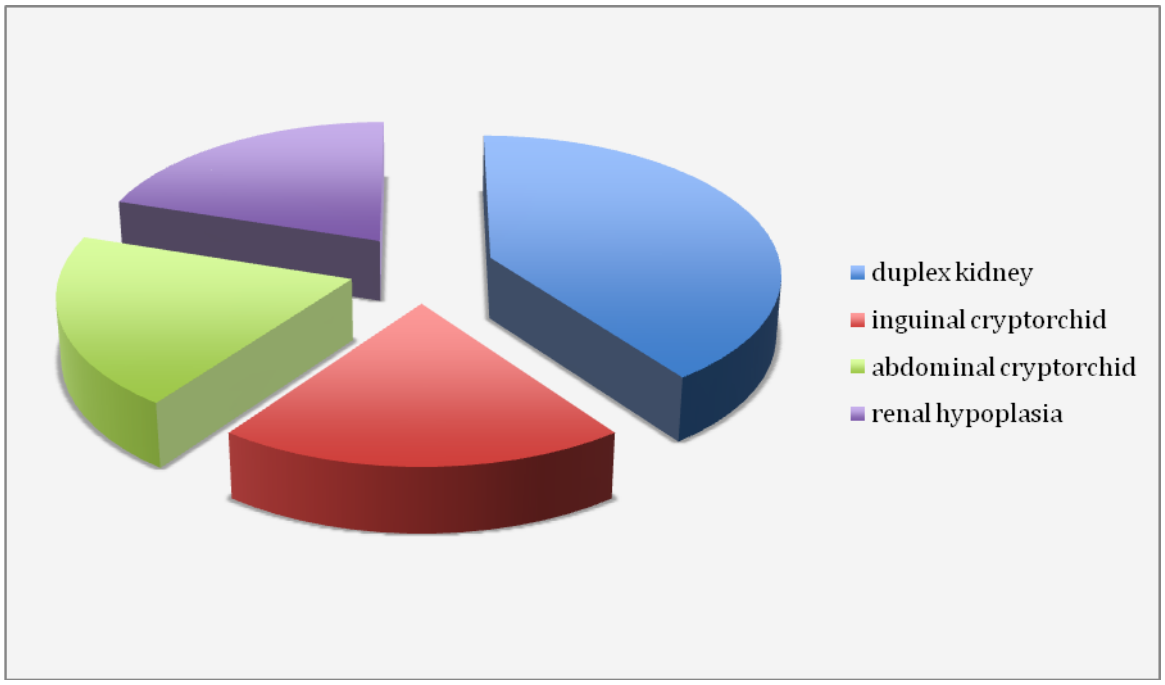

Fig. 2. Structure of congenital malformation of the urinary system in the children under examination

In the structure of congenital defects of the musculoskeletal system, identified in (8.1 ± 3.2)% of the children under examination chondrodysplasia was diagnosed in (2.7 ± 1.9)%, and hip dysplasia in (5;4 ± 2.6)% of the cases.

Among the congenital malformations of the respiratory system scattered pulmonary atelectasis were met in (13.5 ± 3.9)% of the cases, this was diagnosed in the children in neonatal units.

Congenital malformations of CNS analyzers were detected in 3 (4.1 ± 2.3)% of the children. In one child congenital retinal vascular anomaly was diagnosed, on which laser photocoagulation of avascular zones was conducted. The anomaly of the organ of vision in

this case was combined with heart defect. In 2 children under examination congenital abnormality of the cochlear apparatus was identified.

Respiratory diseases identified in this group of children were manifested with frequent acute respiratory diseases in three children or (4.1 ± 2.3)% which does not exceed the general statistical norm.

To study the effects of different factors in the occurrence of defects and developmental abnormalities the analysis of anamnestic data was carried out (Table.) The results obtained allowed to determine the importance of certain anamnestic factors with taking into account somatic and reproductive mothers' health in the development of congenital malformations in children born after induced pregnancy.

Table

Features of obstetric, gynecologic and somatic anamnesis of the mothers' of the mothers of surveyed children

The index under study	Children born after ART		p
	Lack of congenital malformations	Presence of congenital malformations	
Mother's age over 35 y.o.	16.1 ± 4.9	38.9 ± 11.5	0.04
Extra genital pathology	8.9 ± 3.8	44.4 ± 11.7	0.001
Anemia of pregnant	1.8 ± 1.8	16.7 ± 8.8	0.01
Chronic pathology of	-	11.1 ± 7.4	0.01
Chronic pathology of digestive tract	5.4 ± 3.0	5.6 ± 5.4	0.97
Persisting viral infection	5.4 ± 3.0	16.7 ± 8.8	0.12
Obstetric-gynecologic past history	67.9 ± 6.2	77.8 ± 9.8	0.42
Inflammatory diseases of pelvic organs	8.9 ± 3.8	27.8 ± 10.6	0.04
Miscarriages	17.9 ± 5.1	33.3 ± 11.1	0.165
Threatened miscarriage	28.6 ± 6.0	55.6 ± 11.7	0.03

Maternal age had a great influence on the occurrence of malformations ($\chi 2 = 4.18$; $p = 0.04$*),* and this is in agreement with the existing studies pointing to the reduced fertility in women older than 30 years old, as well as regression of ovarian reserve with violation of

morphological, genetic and biophysical properties of gametes [6]. The presence of extragenital pathology significantly influenced the development of both small and large malformations in children. At the same time the association of anemia during pregnancy ($\chi 2$ = 5.89; p = 0.01), presence of pathologies of the urinary system ($\chi 2$ = 8.4; p = 0.004) has been revealed.

A significant effect on the malformations emergence of persistent viral infection was proved. Despite the lack of significant differences in the comparison groups according to this indicator, the impact on the defects emergence is significant with OR 4.42 (CI 95%, 1.64 - 13.25). Burdened obstetric and gynecological history of the mothers often was observed in the group of children with large anomalies of development, at that the association with the presence of defects was significant ($\chi 2$ = 14.45; p = 0.0001). Also, a high level of association with malformations showed inflammatory diseases of the pelvic organs - $\chi 2$ = 4.14; p = 0.04 and the threat of pregnancy termination - $\chi 2$ = 4.35; p = 0.03 in the history of the mothers of the children under examination.

Thus, the children born as a result of induced pregnancy, high incidence of developmental abnormalities indicates the need of early diagnosis and further dynamic observation by pediatrician, as well as the study of the mothers' health with access to detailed information about their physical and reproductive history, peculiarities of pregnancy.

Conclusions: In the children born with the use of ART, in the structure of birth defects and developmental abnormalities those of cardiovascular, urinary and digestive systems, as well as the musculoskeletal system and sensory organs are the most frequent ones. The incidence of abnormalities is associated with mothers' state of somatic and reproductive health, where the urinary tract pathology (p = 0.004) is the most significant factor.

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