Original Article

Congenital Anomalies in Infants Conceived by Assisted Reproductive Techniques

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Abstract

Background: Many studies show that congenital defects in infants conceived by assisted reproductive techniques (ART) are more than infants of normal conception (NC). The aim of this study is to determine the frequency of congenital anomalies in ART infants from Royan Institute and to compare congenital anomalies between two ART techniques.

Methods: In a cross-sectional descriptive study, 400 ART infants from Royan Institute who resided in Tehran were selected by non-random, consecutive sampling. Infants were examined twice (until 9 months of age) by a pediatrician.

Infants' congenital anomalies were described by each body system or organ and type of ART. Data were analyzed by SPSS version 16 and Fisher's exact test.

Results: The frequency of different organ involvement in the two examinations were: 40 (10%) skin, 25 (6.2%) urogenital system, 21 (5.2%) gastrointestinal tract, 13 (3.2%) visual, and 8 (2%) cardiovascular system. Major congenital defects in infants conceived by in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) were hypospadiasis, inguinal hernia, patent ductus arteriosus plus ventricular septal defect (PDA + VSD), developmental dysplasia of the hip, lacrimal duct stenosis during the first year of life, hydronephrosis and urinary reflux over grade III, undescending testis, ureteropelvic junction stenosis, and torticoli.

Conclusions: Two-thirds of ART infants had no defects. A total of 7% of IVF and ICSI infants had one of the major abovementioned congenital anomalies. This rate was higher than NC infants (2%–3%). There was no difference between the ICSI and IVF group.

Keywords: Assisted reproductive techniques, congenital anomalies, infants, intracytoplasmic sperm injection (ICSI), *in vitro* fertilization (IVF)

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Introduction

Many studies have been performed concerning infants conceived by assisted reproductive techniques (ART). In the general population, 3% of surviving neonates have one major congenital anomaly at birth. Some anomalies are detected during childhood or adolescence. The major cause of congenital anomalies are genetic factors which cause 50% of spontaneous abortions during the first trimester of pregnancy and 5% of neonatal deaths.[1] Some factors probably increase the incidence of congenital anomalies in ART infants. For example, natural selection which occurs in normal conception (NC) pregnancies does not occur in ART fertilization. Changes of hormonal status in the lab during the process of mitosis or myosis may cause chromosomal anaploidy. Chemical compounds may also induce point mutations during artificial conception.

Although in European countries congenital anomalies of ART infants are recorded and followed, they could not be compared with the incidence of anomaly in the normal population. The reason for higher incidence of congenital anomalies in ART infants is due to the careful, continuous examination of these infants in comparison with normal infants. Some anomalies such as small umbilical hernias and pigmented skin spots or ear tags, which may not be reported in normal infants, are reported in ART infants.[2]

Many centers that follow up ART infants report a higher incidence of hypospadiasis and undescended testes in these infants.[3] One of the major biases is careful sonography of these infants during pregnancy. In 1990, one center in the United States reported a high incidence of periventricular cysts in the brain, hydronephrosis and unilateral agenesis of the kidneys in these infants, which could not be detected by physical examination.[4]

In many countries only birth time anomalies are recorded, however many anomalies such as pyloric stenosis appear later.[2]

Another reason for increased reporting of more anomalies in ART infants is the precise reporting of these anomalies in the aborted ART fetus or neonate in comparison to the normal population. We could not compare ART infants with normally conceived infants.[5]

The only comparable group with ART infants are those parents became fertile by other techniques, such as ovulation induction. However there are few studies about these infants.

The other confounding factors are the higher age of these couples. In older mothers (27–28 years old) who request ART,[6] the probability of abortion[7,8] or aneuploidy increases[9,10] and Mendelian mutation incidences increase in ART infants of older fathers.[10–12]

Many studies have reported more congenital anomalies in the ART methods, particularly *in vitro* fertilization (IVF) infants, in comparison to natural conception (NC) infants, which is related

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Table 1. Prevalence of organ and system anomalies in ART infants.

ART method	IVF		ICSI		ART	
Systems or Organs	**Number**	**Percentage**	**Number**	**Percentage**	**Number**	**Percentage**
Normal	52	67.5	215	66.5	267	66.7
Skin	6	7.8	34	10.5	40	10
Urogenital	6	7.8	19	5.9	25	6.2
Gastrointestinal	3	3.9	18	5.5	21	5.2
Visual	1	1.3	12	3.7	13	3.25
Cardiovascular	3	2.6	5	1.5	8	2
Limbs-bones	2	2.6	6	1.8	8	2
Endocrine	3	3.9	3	0.9	6	1.5
Otolaryngeal	—	—	5	1.5	5	1.2
Blood and lymphatic	1	1.3	3	0.9	4	1
Nervous	—	—	3	0.9	3	0.75
Abnormal (total)	25	32.5	108	33.4	133	33.3
Total	**77**	**19.2**	**323**	**80.8**	**400**	**100**

Table 2. Prevalence of major anomalies in ART infants.

ART method	IVF		ICSI		ART	
Disease	**Number**	**Percentage**	**Number**	**Percentage**	**Number**	**Percentage**
Inguinal hernia	1	13،	4	1.2	5	1.2
Undescended testis	0	0	2	0.6	2	05،
UPJ stenosis	0	0	1	0.3	1	0.2
Hypospadiasis	1	1. 3	4	1.2	5	1.2
Hydronephrosis and reflux	2	2.6	1	0.3	3	0.7
Severe PDA + VSD	2	2.6	1	0.3	3	0.7
Lacrimal duct stenosis	1	1.3	3	0.9	4	1
DDH	2	2.6	2	0.6	4	1
Torticoli	0	0	1	0.3	1	0.2
Total anomalies	9	11.7	19	5.9	28	7
Total	**77**	**19.2**	**323**	**80.8**	**400**	**100**

Table 3. Prevalence of congenital anomalies in IVF and ICSI infants in different countries.

Country	Congenital anomaly in IVF infants (%)	Congenital anomaly in IVF infants (%)
Iran	5.9	11.7
Belgium[50]	4.2	4.5
Australia[48]	8.6	9
Sweden[46]	8.6	8.1
Norway[51]	3.1	3

to multi-fetal pregnancy and prematurity.[13–18]

In more invasive methods, particularly intracytoplasmic sperm injection (ICSI) in which sperm does not pass its natural way and natural selection deletion does not occur (in an oligospermic man), more chromosomal anomalies have been seen. Other interventions also used in IVF are the gonadotropin stimulator, oocyte aspiration, and culture media, which probably increases the incidence of congenital anomalies.[19,20]

In Iran many infants are conceived by ART, however there are no Iranian studies about congenital anomalies. The aim of this study is the determination of congenital anomalies and distribution rate of organ and system defects of these anomalies in a comparison of infants conceived by different ART methods.

Materials and Methods

In a cross-sectional descriptive study, 400 ART infants from Royan Institute who were residents of Tehran were examined during 22 month in the Child Health and Development Research Center. This study was approved by the Ethics Committee of the Academic Center for Education, Culture and Research (ACECR) and Royan Institute.

This was a non-random, consecutive sampling due to the limited number of available infants which did not allow us to sample randomly. Infants were examined twice, at birth to 6 months and from 6 to 9 months by a pediatrician. Congenital anomalies of infants were classified by body organs or limb involvement and divided into 10 groups by ICD-10 (International Classification of Disease) classification. If the anomaly was not exactly diagnosed by physical exam, sonography, radiography or echocardiography were used.

Data were analyzed by SPSS version 16 and Fisher's exact test.

Results

A total of 208 (52%) boys and 192 (48%) girls were examined. The prevalence of congenital anomalies according to organ or system involvement and ART method are shown in Table 1. Skin anomalies were: 3 (0.75%) hemangioma, 19 (4.7%) umbilical hernia, 7 (1.7%) eczema, 4 (1%) skin hyperpigmentation, 2 (0.5%) semian line, and 5 (1.2%) inguinal hernia. Anomalies seen in the urogenital system were: 1 (0.2%) microlitiasis, 7 (1.7%) hydrocele of the testis, 5 (1.2%) labia adhesion, 1 (0.2%) micropenis, 2 (0.5%) undescended testes, 1 (0.2%) ureteropelvic junction (UPJ) stenosis, 5 (1.2%) hypospadias, 3 (0.7%) renal reflux and hydronephrosis. Gastrointestinal anomalies were: 1 (0.2%) constipation, 11 (2.75%) gastro-esophageal reflux, 5 (1.2%) prolonged icter, and 4 (1%) thrush.

In the cardiovascular system there were 8 (2%) patent ductus arteriosus ± ventricular septal defect (PDA + VSD); visual anomalies were: 4 (1%) stenosis of the lacrimal duct, 3 (0.75%) conjunctivitis, and 6 (1.5%) strabismus. Orthopedics were: 4 (1%)

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developmental dysplasia of the hip (DDH), 1 (0.2%) torticoli, 1 (0.2%) spina bifida, and 2 (0.5%) pes varus.

The otolaryngeal system anomalies were 3 (0.7%) lingual frenulum, 1 (0.2%) hearing loss, and 1 (0.2%) ear deformity. In the blood and lymphatic system there were 1 (0.2%) anemia, 1 (0.2%) lymphadenitis, and 2 (0.5%) G6 PD. Nervous system anomalies included 3 (0.7%) infants with cerebral palsy (CP), and finally the endocrine system anomalies were: 3 (0.7%) hypothyroidism and 3 (0.7%) rickets.

According to ICD-10, hypospadiasis, inguinal hernia, severe PDA + VSD, stenosis of the lacrimal duct until age one year, urethral reflux more than grade III and hydronephrosis, undescended testis (until one year of age), UPJ stenosis, torticoli, and DDH, which requires surgery are all considered major anomalies. Anomalies in Table 2 are classified according to major anomalies and ART technique.

Discussion

The major problem in classification of congenital anomalies is the definition of a major anomaly. In this study all anomalies that required surgery, until one year of age or a disturbed function of the organs have been considered major congenital anomalies.

Of ART infants who were examined twice, one-third had congenital anomalies. IVF infants had higher numbers of congenital heart diseases, DDH and hydronephrosis with renal reflux (Table 2).

A higher prevalence of congenital anomalies were seen in the skin (10%), urogenital (6.2%), gastrointestinal (5.2%), visual (3.2%), and cardiovascular systems (2%).

However, the prevalence of inguinal hernia was 1.2%, which was lower than term (3%–5%) or preterm (9%–11%) NC infants.[21] There were no significant differences in the prevalence of inguinal hernias in both groups ($P = 1$).

The prevalence of major anomalies in the urogenital system in IVF infants was 7.8%, whereas for ICSI infants it was 5.9%. In the another study the prevalence of major anomaly of urogenital system were 3.9% and 2.5% (in IVF and ICSI infants, respectively) which was not significant ($P = 0.45$) with each other and other studies (3% in IVF and 5% in ICSI).[22]

Gastrointestinal anomalies were seen in 5.2% of infants; all of which were classified as minor anomalies, the higher rate seen in ICSI infants compared to the IVF group.

Major anomalies of the cardiovascular system were seen in 0.7% of infants, which was similar to the general population (0.8%).[23] However, it was not significantly different between the two groups ($P = 0.09$).

A total of 3.2% of infants had visual anomalies, which was higher in the ICSI group ($P = 0.57$). In one study, this was reported as 0.9%–4.2% in IVF infants[24]; other studies reported no differences between ART infants and the control group.[22,25–28] In the general population,1.6% of infants needed lacrimal duct stenosis surgery,[29] which was 1% in our study.

There were 2% of infants who had either limb or bone anomalies, which was not different between the ICSI and IVF infants ($P = 0.17$). The prevalence of DDH in our study was 1%, the same as seen in the general population (0.8%–1%).[30]

Congenital anomalies of the otolaryngeal system were seen in 1.2% of infants; sensory hearing loss was 0.2%, which was reported only in ICSI infants and did not differ with respect to the prevalence of sensory hearing loss in NC (0.5–1 in 1000 infants).

Regarding nervous system defects, there were 3 (0.7%) CP infants conceived by ICSI which was higher than the prevalence in the general population (0.2%).[31] In other studies, the prevalence of CP in ART infants was 4 times,[24] 1.6 times,[32] and 1.8 times[33] more than NC infants. In 5 studies, no significant differences were noted between ART and NC infants in nervous system anomalies.[25,26,34–36] In all studies, the most common reason for CP in these infants was prematurity and low birth weight.[36,37] There was no significant difference in the prevalence of CP in ICSI and IVF infants in our study ($P = 1$).

Congenital hypothyroidism was (0.7%) in our study and 0.1% in Tehran's neonate population.[38] There were no differences between the two groups of ART infants ($P = 1$).

In general, one-third of ART infants had either one minor or major anomaly and 7% had one of the major congenital anomalies, which was higher when compared with the general population (2%–3%).[1,39] This prevalence was similar to a study in Finland (5.5%–6.6%)[40,41] and higher than the prevalence of major congenital anomalies in the Netherlands (2.3%, 3.7%),[42,43] England (4.8%),[44] Australia (4.3%),[45] and Sweden (5%).[46]

In comparison with other studies, Germany (8.6%)[47] and Australia (8.9%),[48,49] had lower prevalences.

In our study the percent of major congenital anomalies among ICSI (5.9%) and IVF (11.7%) infants was not significantly different between the two groups ($P = 0.08$).

In 4 studies on IVF and ICSI infants in other countries, there were no reported significant differences between the two groups regarding major congenital anomalies (Table 3).

In our country, after more than one decade of infants born via ART, there were no studies on congenital anomalies and the comparison to NC infants. The results of two examinations of ART infants until 9 months of age showed that two-thirds were normal, 7% had one major anomaly, which was 3 times more than the general population and there was no significant difference between ICSI and IVF infants.

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