Ocular Manifestations in Infants Resulted from Assisted Reproductive Technology (ART)

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Abstract

Objective: Nowadays, many infertile couples can have child by assistant reproductive technology (ART). Always the undesirable effects of these methods on newborn are considered and are evaluated. The aim of this study is to describe the impact of ART on ocular and visual performances of infants born by these methods.

Materials and methods: In a cross-sectional descriptive study, 479 infants aged three-nine months presented to an optometry clinic of Child Health and Development Research Department (CHDRD), Tehran, Iran. Static retinoscopy, qualitative fixation evaluation, Hirschberg test, red reflex assessment and external eye examination were carried out. Other information such as birth weight and maturity of the infants was recorded.

Results: It was possible to assess only 320 out of 479 infants due to general condition of some participants. Comparison of mean refractive error in infants' right and left eyes did not show any significant difference. Our findings confirmed that 20.3% had poor fixation, while 2.9% revealed manifest strabismus. The results also revealed the prevalences of myopia, hyperopia and emmetropia are 2.9%, 87%, and 10.1%, respectively. Red reflex abnormalities were significantly found in boys and in preterm infants ($p<0.05$). Failure of fixation control was seen more frequently with increasing refractive error, which significantly developed in preterm infants ($p<0.001$).

Conclusion: These results reflect the necessity of more comprehensive assessments and further follow-up of infants born by ART, especially for premature male ART infants. These results also suggest the probability of fixation condition and visual deficiencies in these infants. It is recommended to pay close attention to this preliminary report about the refractive and fixation condition of the infants born after ART.

Keywords: Assisted Reproductive Techniques (ART), Infants, Optometry, Visual Acuity

Introduction

Recent scientific advances have provided the possibility of fertility for infertile couples. Scientists and parents of the children born by such interventions are always faced with the concern that how their child's visual health will be. Unfortunately, despite extensive researches in the field of assisted reproductive technology (ART), particularly in Iran, comprehensive studies on ophthalmic health and integrity of visual reflexes in such infants have not been done yet. With regard to the fact that these infants are born after several years of treatment and

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spending high costs, assessment and monitoring of ART infants is necessary.

Development of the visual system begins during embryonic period and continues until after birth (1). Correct and complete development of the human visual system is affected by several intrinsic and extrinsic factors (2). Infants born by ART may be susceptible to several factors with undesirable effects on development of the visual system (3). On the other hand environmental conditions, before and after birth, strongly influence infant's visual system (4). Hence, being aware of their visual system condition can help the professionals to choose the proper technique for assisted reproduction technology and the effective care for it. Furthermore, a child's first 12 month of life is considered as the critical period (5); although, some studies have stated that the development of the visual reflexes may continue after age three (6). Appropriate interventions in this period of time can reduce the influence of interruptive factors affecting the visual system development (7). Therefore, as a rule in visual sciences, all infants experiencing hazardous conditions during prenatal period and those with unfavorable hereditary background must undergo various eye exams during infancy (8). Accordingly, several screening programs are designated for this period in many countries (9-11). The aim of this study is to describe the impact of assisted reproductive technology (ART) on ocular and visual performances of infants born by these methods.

Materials and methods

This cross-sectional descriptive study was accomplished at Child Health and Development Research Department (CHDRD) of Academic Center for Education, Culture and Research (ACECR), Tehran, Iran. Ethical considerations of this study were approved by Ethical Committee of Royan Research Institute and ACECR. We used non-random sequential sampling, and recorded history and the information about birth condition of all participants. Then, a representative was giving detailed explanations to the couples admitted to Royan Institute for the ophthalmic examination of their child. The inclusion criteria were infants conceived through one kind of ART methods (IVF, ICSI) and residence in Tehran, if infants did not come for the second examination, they were excluded from study. Infants were brought to the center from the age of one month, but clinical ophthalmic assessment was accomplished after the age of three months. Infants were re-examined to ensure the accuracy of the initial findings at age of nine months.

Their refractive status was evaluated using dry refraction by streak static retinoscopy. As the time consuming nature of cyclorefraction, and also, lack of permission from most parents for using cycloplegic agents, cyclorefraction did not performed.

Furthermore, red reflex assessment, Hirschberg test, qualitative fixation evaluation, and external eye examination were performed. Family profile of the infants was also assessed. Since it was impossible to perform all tests on all infants due to crying, sleeping or their parents' impatience, a total of 320 infants were only evaluated. Infants who needed further assessments and interventions were referred to more specialized centers. Results were analyzed by using SPSS 16 software.

Results

Evaluation of refractive status was possible in 320 infants. Statistical comparison of the obtained results of refractive error between their right and left eyes showed no significant differences. Table 1 demonstrates the results of distribution of ART infants regarding perinatal variable and reproductive techniques.

Among participants, 101 (31.6%) infants and 219 (68.4%) infants were preterm and term, respectively (Table 1).

The findings confirmed 20.3% of the infants had poor fixation, and 2.9% showed manifest strabismus in Hirschberg test. The results also revealed the prevalences of myopia, hyperopia and emmetropia are 2.9%, 87%, and 10.1%, respectively (Table 2). External examination only showed 1% abnormality in infants' eyes. These findings did not show any significant difference between the sexes. But, the result of red reflex testing of participants confirmed abnormality in 17 male (5.3%) compared to 2 female (0.6%) ($p=0.003$), indicating the involvement of male more than female. This abnormality was present significantly in preterm infants (15 cases, 4.7%) than term infants (4 cases, 1.2%) ($p=0.006$). There were 60 preterm infants (18.8%) and 5 term infants (1.5%) with fixation deficiency, which indicates there were significantly more fixation deficient infants among preterm ($p<0.001$). A significant correlation was found between refractive error and poor fixation, so failure of fixation control was observed more frequently with increasing refractive error ($p<0.001$).

Table 1: Distribution of ART infants with consideration of prenatal variables and reproductive techniques

ART Prenatal variables	ICSI	IVF	Total number
Total exam infants	245(76.5%)	75(23.5%)	320(100%)
Preterm	75(23.5%)	26(8%)	101(31.6%)
Term	170(53.1%)	49(15.3%)	219(68.4%)
Low birth weigh	91(28.4%)	20(6.2%)	111(34.6%)
Appropriate for gestational age	154(48.1%)	55(17.2%)	209(65.3%)

IVF: In vitro fertilization ICSI: Intra cytoplasmic sperm injection

Table 2: Comparison the relations between the descriptive results of red reflex, fixation deficiency and refractive error and sex and maturity of ART infants

Maturity & Sex Eye exam	Sex		Maturity		Total
	Boys	Girls	Preterm	Term	
Total	157(49%)	163(51%)	101(31.6%)	219(68.4%)	320 (100%)
Abnormal red reflex	17 (5.3 %)	2 (0.6 %)	15 (4.7%)	4 (1.2%)	19(5.9%)
Normal red reflex	140(43.7%)	161(50.4%)	86(26.9%)	215(67.2%)	301(94.1%)
Fixation deficient	37(11.5%)	28 (8.8%)	60 (18.8%)	5 (1.5%)	65(20.3%)
Fixation normal	120(37.5%)	135(42.2%)	41(12.8%)	214(66.9%)	255(79.7%)
Refractive error (myopia)	5 (1.5%)	4 (1.3%)	7 (2.2%)	2 (0.7%)	9(2.9%)
Refractive normal (hyperopia,emmetropia)	152(47.5%)	159(49.7%)	94(29.3%)	217(67.8%)	311(97.1%)
Astigmatism	58(47.1%)	65(52.8%)	82(66.6%)	41(33.3%)	123(38.6%)

Discussion

Our results reflect the necessity of more comprehensive assessments and further follow-up of infants born by ART, especially for premature male ART infants. These results also suggest the probability of fixation condition and visual deficiencies in these infants. Many studies have demonstrated that low birth weight and/or premature neonates have higher refractive errors than full term neonates (12- 14). Environmental influences besides hereditary factors may affect birth weight (3, 4, 15, 16). So, infants born by ART may have special genetic background and environmental conditions, which make them different than naturally conceived infants (3, 4, 15, 16). But, this study showed most of the ART-conceived neonates were not underweight and preterm (Table 1). Our finding confirmed that prevalence and severity of refractive errors in ART infants are caused by the factors involving in ART. These factors can influence ART infants in fetal period are laboratory environment, temperature, chemical materials, drugs for ovulation induction and drugs for continuity of pregnancy. However, the assisted reproductive technologies have been introduced only a few years ago, and there are not enough scientific reports regarding visual health of these infants. One of the most important studies in this field belongs to the Anteby et al. (2001) (17). Their study was conducted on 47 boys and girls aged two months to five years born after *in vitro* fertilization (IVF) (82 eyes). Their results revealed the prevalences of myopia, hyperopia and emmetropia were 16%, 57%, and 27%, respectively. They performed cycloplegic refraction testing, and the result showed higher prevalence of hyperopia in comparison to prevalence of myopia. Nevertheless, in our findings showed that the prevalences of myopia, hyperopia and emmetropia are 2.9%, 87%, and 10.1%, respectively. Also, higher prevalence of hyperopia in our study in comparison to that in study of Anteby et al. may be due to either racial and genetic differences of two populations or differences in techniques used for ART (17-25). Changes in genetic background along with environmental influences can make significant differences in refractive status of newborn infants. Analysis of ocular and visual data of Iranian infants less than one year of age would be very helpful to come to a certain conclusion but unfortunately, there was not any research on infants and very young children in Iran. However, the studies that have been done in Tehran and Dezful cities by Fotohi et al (2007) may estimate the refractive status in some Iranian populations (26).

The result of study conducted in Tehran showed that among children over five years of age, there were 17.2% myopia and 56.5% hyperopia. While the result of study conducted in Dezful revealed that myopia was 3.4% and hyperopia was seen in 16.6% of the children between 7 to 15 years, indicating refractive error incidences were significantly different than our study. Therefore, considering decreasing of prevalence of hyperopia with age and emmetropization mechanism, different incidences of refractive error may be expected to happen in different ages (26). However, precise conclusion may not be attainable in this regard.

The rate of astigmatism was 23.9% in Tehran and 18.7% in Dezful, whereas our result showed the rate of 38.6%.. Other studies in other countries mostly show lower prevalence for astigmatism. Axer et al. (2005) found no difference in incidence of astigmatism between IVF and naturally conceived infants (3). In a study by Wikstrand (2006) on visual function and ocular morphology in children born after intra-cytoplasmic sperm injection (ICSI), he has demonstrates that there is no significant difference between ICSI and control group in the obtained results of performed following tests: hyperopia, myopia, astigmatism, heterotropia, stereo acuity, and convergence (18).

In another study by Varghese et al. (2009), they examined the correlation of refractive error with birth weight, head circumference and birth age (20). Their findings show a significant correlation between physical parameters of development and refractive status. They strictly recommend screening of refractive error for the infants who do not meet the criteria in developmental parameters. Management of refractive error in these infants can prevent many further visual defects. It is obvious that one of the main consequences of uncorrected refractive error, especially astigmatism, is amblyopia. In a study by Ludwig (2010), he compared vision and hearing function between children in ICSI and control groups, and did not find any significant difference between these two groups (27).

Basatemur et al. (2010) compared children conceived by IVF or ICSI with age matched naturally conceived children and found no significant difference regarding developmental parameters (28). Nevertheless, in study by Basatemur (2010) and other similar studies have stated that further researches are needed for certain judgment (28, 29). It seems that more precise conclusion regarding refractive status of Iranian ART infants is required in order to gather sufficient information about normal infants (ART and naturally conceived infants) less than one year of age.

In our study, external examination of the eyes indicated abnormality in about 1% of the participants. This result seems better in comparison to some other studies (1% vs. 8.22%) (30).

Our findings also confirmed that incidence of red reflex abnormality was significantly more in boys than in girls. Red reflex abnormality may be due to high refractive error, media opacities or retinal defects (31-33). Examinations showed no significant difference in refractive error between boys and girls, so the difference found in incidence of red reflex abnormality may be due to media opacities or retinal defects (31, 34). Other studies showed no difference between boys and girls regarding media opacities and retinal defects. However, in a study by Eckstein et al. (1996), they stated that the reason of higher incidence of cataract in boys is due to a higher rate of boys referred to eye clinics. This is a scientific article, so has to be based on findings, documents and reasonable explanation.(35-37). Nevertheless, sex dependent genetic disorders may show higher incidence in one sex, so these conditions may cause abnormalities in ocular media, retina, as well as changes in red reflex.

In another study by Bhatti (2003), he confirmed the higher prevalence of cataract in premature infants (37), which is in agreement with our result that red reflex abnormality was significantly more common among premature infants.

Another parameter assessed in our study was ocular motility. We found that 20.3% of infants had poor fixation control. Unlike studies by Pedroso (2003) and Robaei (2006) on naturally conceived infants, our results showed that ocular reflexes of ART infants were not so desirable (38, 39). We found a significant difference in fixation control between premature and full-term infants. Premature infants had significantly poorer fixation control, which is a result of visual problems. In other words, health and integrity of visual system is necessary for proper fixation. Some studies have indicated that premature infants can have proper fixation control as in full-terms (40, 41). Nevertheless, other studies have demonstrated that premature infants have problem in fixation control in spite of their success in other visual and psychophysical examinations. In our study, disability to control fixation significantly increased with increasing refractive error in ART

infants. This can be due to the fact that deterioration of visual acuity which is the result of high refractive error leading to undesirable effect on infant's fixation function (42).

After performing Hirschberg test, we found that 2.9% of ART infants were afflicted with manifest strabismus. In other study on Iranian population by Fotouhi et al (2007), the prevalence of strabismus among children over five years old was about 0.8% (26). In a study by Anteby et al. (2001) on ART infants, the prevalence of strabismus was declared about 4% (17). Another study by Robaei et al. (2006) on Australian children population demonstrated that exo and eso deviations had different incidence rates (39). They found significant correlation between prematurity and incidence of strabismus. Therefore, it seems that infants born after ART are more likely to have strabismus because of prematurity and their lower birth weight. However in this study, we did not find strabismus among participants. Binocular reflexes of these infants had not been completely developed, and it was possible that some of them would have better binocular condition in the future (39). Using more accurate motility testing methods, like cover test, could lead to more reliable results, but it was not possible to perform cover test due to the age of the infants.

Although some scientists did not find any differences in ocular and visual conditions between ART and naturally conceived infants (3,17), special conditions of ART infants may affect development of the visual system, so some other scientists recommend vision screening for these infants (18,23,25).

Conclusion

These results clearly reflect the necessity of more comprehensive assessments and further follow-up of infants born by ART, especially for premature male ART infants. These results also reflect the likelihood of finding refractive error in these children in older ages, and also, suggest the probability of fixation and visual deficiencies in these infants. It is recommended infertility specialists, ophthalmologists, optometrists, pediatricians, and parents of ART children to pay close attention to this preliminary report about the refractive and fixation condition of the infants born after ART.

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