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## Comparison of Birth Defects in Infants Conceived by Assisted Reproductive Technologies vs. Naturally Conceived Infants in Mashhad, Iran

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### Abstract

**Background:** Assisted reproductive technologies (ART) are known as a treatment for infertility in which oocyte undergoes manipulation outside body. The aim of this study was to study the evaluation of birth defects in infants conceived through assisted reproductive technologies (ART) and compare them with naturally-conceived infants. **Materials and Methods:** In this retrospective study, four hundred naturally-conceived infants and 400 infants conceived by ARTs between 20 March and 20 November 2012 in Gha'em Hospital and Sheikh Hospital of Mashhad in Iran participated in this study. Infants were evaluated by a pediatrician at the time of birth, 10 days and 40 days after birth. Correlation between the use of IVF and/or ICSI methods and birth defects was evaluated. **Results:** Of total 800 infants (450 boys and 350 girls), half of the infants were conceived through natural pregnancy, 200(25%) through in-vitro fertilization (IVF) and 200 (25%) intra- cytoplasmic sperm injection (ICSI). In Infants conceived by IVF, 5 cases (2.5%) had a kind of birth defect just similar to those conceived by ICSI; while 4 cases had birth defects in natural pregnancy. There was no significant correlation between the use of IVF and/or ICSI methods in terms of birth defects ( $P=0.280$ ). **Conclusion:** We found that using IVF or ICSI methods is not associated with increasing birth defects. [GMJ.2015;4(4):146-50]

**Keywords:** Assisted Reproductive Technologies (ART); In Vitro Fertilization (IVF); Intra Cytoplasmic Sperm Injection (ICSI); Birth Defects; Congenital anomalies.

### Introduction

Assisted reproductive technologies (ART) are known as a treatment for infertility in which oocyte undergoes manipulation outside body. In vitro fertilization (IVF) and Intra cytoplasmic sperm injection (ICSI) are the most common methods of ARTs. Nowadays, these methods are used widely all around the world such as the United States of America (USA) with more than 134000 ARTs in 2005 resulting in 52000 births, about 1% of American

population. There are about 4000000 infertile couples in Iran predicted to increase by 25000 every year [1].

However, studies on the long and short-time effects of ARTs on the health of newborns are not as much as rapid progresses in infertility treatment. It has remained a question if ARTs can lead to more birth defects rather than natural pregnancies since the invention of these methods.

Previous studies in various parts of the world had different results; some studies concluded

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that there are more birth defects induced by ARTs [2]. Others reported a similar rate of birth defects in infants conceived by ARTs and those by natural pregnancies [3, 4]. Regarding these results, we aimed to assess birth defects in infants conceived by IVF and ICSI in comparison with those conceived by natural pregnancies.

### Materials and Methods

This retrospective study was conducted between 20 March and 20 November 2012. Four hundred infants, conceived by natural pregnancies during this period, were selected using convenience sampling method in Gha'em Hospital and Sheikh Hospital of Mashhad in Iran.

All infants who were conceived by IVF or ICSI in "Mashhad Montaserieh Center of Infertility Treatment" between March 2006 and February 2012 were assessed. Their parents were asked to answer a questionnaire including age of couples including: 20-25 years, 26-30 years, 31-35 years and 36-40 years, previous pregnancy history, abortion history, personal and family history of infant born with birth defects including: cardiac anomalies, esophageal atresia, anorectal atresia, hypospadias, ureterovesicular junction obstruction (UVJO), cleft lip, cause of infertility, type of treatment and singleton or multiple pregnancies by reviewing previous medical records. Parents were asked to return to the hospital with their babies. The result of evaluations by pediatrician at the time of birth, 10 days and 40 days after birth and birth defects were also recorded in hospital notes. In the present study, most birth defects were diagnosable except heart septal defects which were recommended echocardiography in case of probability.

We considered a parental age between 20 and 40 and non-familial marriage as inclusion criteria. Cases with a positive history of repeated abortion and family history of fetal anomalies were excluded from this study.

### Statistical Analysis

Data were analyzed using statistical package for social sciences (SPSS) version 16 (SPSS Inc. Chicago, IL) for windows. Normal dis-

tribution variables (approved by one-sample Kolmogorov-Smirnov test) were compared using independent sample t-test between the groups and paired sample t-test within the groups. Chi square test also was used to compare categorical variables in the two groups. A P-value of less than 0.05 was considered statistically significant.

### Ethical Considerations

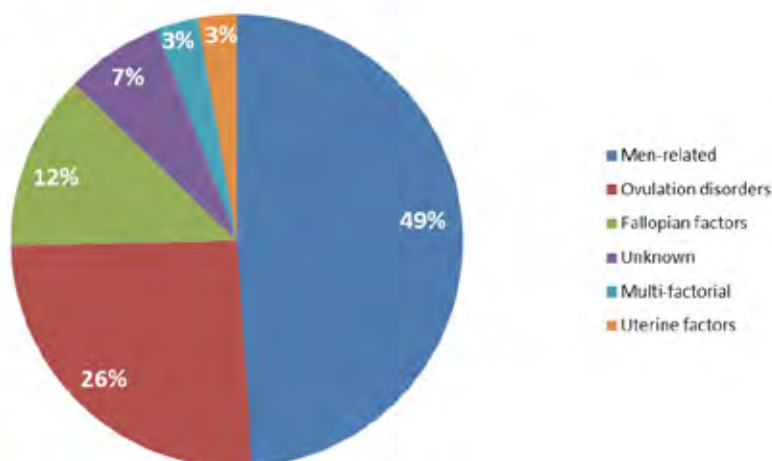
This study was approved in ethics committee of Mashhad University of Medical Sciences and Health Services. Individuals were asked to sign an informed consent before answering the questionnaire. All terms of Helsinki declaration were considered and the personal information remained anonymous.

### Results

Of 800 cases (450 boys and 350 girls) analyzed, 200 (25%) infants were conceived through IVF, 200 (25%) by ICSI and 400 (50%) by natural pregnancy. Among them, 117 (14.6%) infants were born between weeks 28-36 and 683 (85.4%) between weeks 37-40 of pregnancy. In both spontaneous and ART (by IVF or ICSI) pregnancies, most of the infants were born between weeks 37 to 4 (Table 1). There was no significant difference between groups for gestational age ( $P=0.547$ ). Men-related problems (48.9%) and ovulation disorders (25.7%) were the main causes of infertility. While multi-factorial etiologies were the least common causes of infertility (3%) (Figure 1). In both groups, a majority of pregnancies were singleton; 97.3% in natural and 65% in ART group (Table 2). While twin (30.5%) and triplet (4.5%) pregnancies were more frequent in ART group. There was a significant relation between multiple pregnancies and ARTs ( $P<0.001$ ).

**Table 1:** Distribution of Birth Age in Groups

Study Group	Weeks 28-36	Weeks 37-40	P Value
Natural pregnancy	55(13.7%)	345(86.3%)	0.547
IVF or ICSI	62(15.5%)	338(84.5%)	



**Figure1:** Frequency of Infertility Causes in ART Group

**Table2:** Distribution of Pregnancies in both Spontaneous ART Group

Study Group	Single Pregnancies N(%)	Twin Pregnancies N(%)	Triple Pregnancies N(%)	P Value
Natural Pregnancies	389(97.3%)	8(2%)	3(0.7%)	<0.001
IVF or ICSI	260(65%)	122(30.5%)	18(4.5%)	

In mothers who underwent IVF, 152 (76%) cases had no history of previous pregnancy while it was 183 (91.5 %) for ICSI. The age of cases treated by IVF or ICSI ranged between 26 and 30 most frequently (40.5 % in both) but those with spontaneous pregnancy were mostly between 20 to 25 years of age. A significant association is seen between the use of IVF or ICSI and higher age of mothers (P=0.00).

Male infant number was larger than females in mothers treated by whether IVF (54.5%) or ICSI (57.5%) as well as those with natural pregnancy (56.5%) (Figure2).

In infants conceived by IVF, 5 cases (2.5%) had a kind of birth defects just similar to those conceived by ICSI (Table 3).

Only 4 cases had birth defects in natural pregnancy. There was no significant correlation between the use of IVF and/or ICSI methods and birth defects (P=0.28).

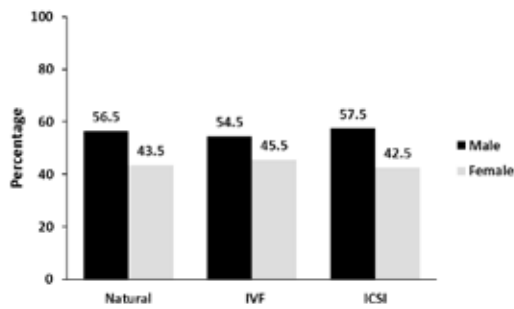
Two (1%) cases in IVF group and 1 (0.5%) in ICSI group had cardiac anomalies.

No esophageal atresia appeared in IVF group while ICSI and natural pregnancy groups had one case each. Among infants conceived by IVF, there was a (0.5%) case of anorectal atresia. Hypospadias presented in 1 % of IVF group cases and 0.2 % of natural pregnancies. One infant in IVF group had UVJO. Cleft lip and cleft palate involved one case (0.5%) in IVF, one (0.5%) in ICSI and two (0.5%) cases in natural pregnancies.

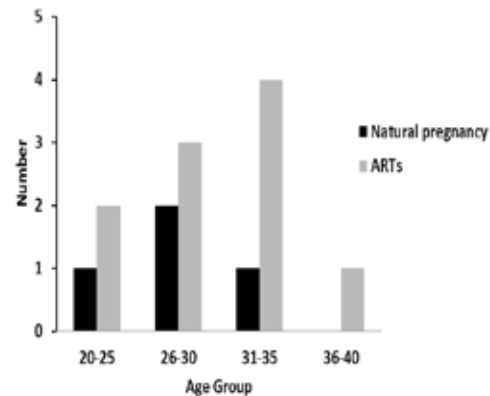
Figure 3 demonstrates the distribution of birth defects based on mothers' age group and their relations. There is no significant association between birth defects and age of pregnancy in both ARTs and natural pregnancy groups.

Only 4 mothers out of 800 had a history of infants born with birth defects in their family. In the present study, all infants with birth defects were negative for this history.

There was no significant correlation between positive history for birth defects in the family and infants with birth defects in this study.



**Figure2.** Distribution of Gender based on Pregnancy Methods



**Figure3.** Distribution of Congenital Anomalies based on Mothers' Age

**Table3:** Congenital Anomalies based on Pregnancy Methods

Method of Pregnancy	Birth Defects N(%)	Without Birth Defects	P Value
IVF or ICSI	10(2.5%)	390(97.5%)	0.28
Natural	4(1%)	396(99%)	

**Discussion**

We found that using IVF or ICSI methods had no direct effect on birth defects in infants conceived by these methods. In the present study, a majority of infants were born at term gestational ages in both spontaneous and ART groups. Our findings showed that applying ART methods are more associated with twin and triplet pregnancies. We also found that ART methods are applied in mothers with higher ages rather than spontaneous pregnancies.

Previous studies on the rate of birth defects induced by IVF or ICSI showed different results; certain studies have reported ARTs as a predisposing factor for birth defects and some have denied it.

Han *et al.* (Shanghai, China) [3] concluded that general prevalence of birth defects in infants conceived by ARTs is similar to those born naturally. They also reported that high age of mother and multi parity increase the risk of birth defects. While in the present study, we found no correlation between mother's age and birth defects.

According to Hansen *et al.* [5], who conducted another study between 1993 and 1997, ARTs are associated with a double risk of birth defects. While Olson *et al.* in a retrospective study and Rimm *et al.* [6, 7] in a Meta-analysis concluded that infants conceived by IVF had a slightly more birth defects; however, it was not statistically significant which is in concordance with our study.

In another study, Sagot *et al.* [2] compared infants conceived by IVF and intrauterine insemination (IUI) with those conceived naturally. They concluded that there is a higher prevalence of major congenital malformations after both IVF and IUI technics. EL-Chaar *et al.* [8] also mentioned a significant increase in risk of birth defects following IVF and IUI.

Comparing the obstetric outcomes and congenital abnormalities in pregnancies conceived by IVF, ICSI and in vitro maturation (IVM), Buckett *et al.* [4] reported an increased risk of congenital abnormalities by all ART pregnancies.

Källén *et al.* [9] demonstrated that congenital abnormalities slightly increased after IVF in two different periods of study.

AL-Fifi *et al.* [10] concluded that ICSI conceived pregnancies are not associated with more congenital abnormalities compared to naturally conceived pregnancies and they are also characterized by more gestations and live-born.

In a review article Lu *et al.* [11] mentioned that although a majority of infants conceived by ARTs are normal, there is increasing evidence that they face more poor perinatal outcomes as well as birth defects.

Farhangniya *et al.* [12] also reported a higher risk of major congenital malformations associated with pregnancies resulted from ARTs in Tehran, Iran.

## Conclusion

In conclusion, there is no relation between applying ARTs and increased risk of congenital abnormalities. Future studies with a larger amount of samples are needed.

## Conflict of Interest

We declare that there are no conflicts of interest in terms of the present study.

## References

1. Gurunath S, Pandian Z, Anderson RA, Bhattacharya S. Defining infertility—a systematic review of prevalence studies. *Human Reproduction Update*. 2011;17(5):575-88.
2. Sagot P, Bechoua S, Ferdynus C, Facy A, Flamm X, Gouyon J, *et al.* Similarly increased congenital anomaly rates after intrauterine insemination and IVF technologies: a retrospective cohort study. *Human reproduction*. 2012;27(3):902-9.
3. Han J, Chen H, Niu Z, Sun Y, Sun X, Zhao X, *et al.* [A 10-year survey on birth defects after in vitro fertilization-embryo transfer in Shanghai]. *Zhonghua fu chan ke za zhi*. 2010;45(2):124-7.
4. Buckett WM, Chian R-C, Holzer H, Dean N, Usher R, Tan SL. Obstetric outcomes and congenital abnormalities after in vitro maturation, in vitro fertilization, and intracytoplasmic sperm injection. *Obstetrics & Gynecology*. 2007;110(4):885-91.
5. Hansen M, Kurinczuk JJ, Bower C, Webb S. The risk of major birth defects after intracytoplasmic sperm injection and in vitro fertilization. *New England Journal of Medicine*. 2002;346(10):725-30.
6. Rimm AA, Katayama AC, Katayama KP. A meta-analysis of the impact of IVF and ICSI on major malformations after adjusting for the effect of subfertility. *Journal of assisted reproduction and genetics*. 2011;28(8):699-705.
7. Olson CK, Keppler-Noreuil KM, Romitti PA, Budelier WT, Ryan G, Sparks AE, *et al.* In vitro fertilization is associated with an increase in major birth defects. *Fertility and sterility*. 2005;84(5):1308-15.
8. El-Chaar D, Yang Q, Gao J, Bottomley J, Leader A, Wen SW, *et al.* Risk of birth defects increased in pregnancies conceived by assisted human reproduction. *Fertility and sterility*. 2009;92(5):1557-61.
9. Källén B, Finnström O, Lindam A, Nilsson E, Nygren KG, Otterblad PO. Congenital malformations in infants born after in vitro fertilization in Sweden. *Birth Defects Research Part A: Clinical and Molecular Teratology*. 2010;88(3):137-43.
10. Al-Fifi S, Al-Binali A, Al-Shahrani M, Shafiq H, Bahar M, Almushait M, *et al.* Congenital anomalies and other perinatal outcomes in ICSI vs. naturally conceived pregnancies: a comparative study. *Journal of assisted reproduction and genetics*. 2009;26(7):377-81.
11. Lu Y-h, Wang N, Jin F. Long-term follow-up of children conceived through assisted reproductive technology. *Journal of Zhejiang University Science B*. 2013;14(5):359-71.
12. Farhangniya M, Rabori ED, Kermani RM, Haghdoost AA, Bahrapour A, Bagheri P, *et al.* Comparison of congenital abnormalities of infants conceived by assisted reproductive techniques versus infants with natural conception in Tehran. *International journal of fertility & sterility*. 2013;7(3):217.