

# Infantile Prognosis of Neonates Conceived by Assisted Reproductive Techniques: A prospective Study

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## Research article

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# Abstract

**Introduction:** Outcomes of neonates of infertile couples that are golden babies and care of them is an issue of importance. But it is not yet clear if the prognosis is different between them and neonates from fertile couples. The purpose of this study was to determine the outcome of neonates conceived by assisted reproductive techniques.

**Methods:** In this cohort study, a total of 165 newborn who were conceived by assisted reproductive techniques (ART) and 165 naturally conceived newborns were enrolled. The study was prospective from April 2017 to October 2019. All newborns were examined by neonatologist after birth and their outcome were followed up to two year. The outcomes were compared with neonates from fertile couple using appropriate statistical tests.

**Results:** The preterm neonates (60% vs. 38%) were higher in ART cases ( $P < 0.001$ ). The mean gravid and parity were lower in ART group ( $P < 0.001$ ) and the nulliparity was higher in them. Multiple pregnancies were higher in ART cases (45% vs. 10%;  $P < 0.001$ ). Cesarean section rate was higher (91% vs 67%) in ART cases ( $P < 0.001$ ). Pre-eclampsia rate was higher in ART cases (16 % vs. 6%;  $P = 0.004$ ). Female sex was higher in ART group ( $P = 0.035$ ). Birth weight was significantly lower in ART group ( $P = 0.002$ ) and the Apgar was also lower ( $P = 0.002$ ;  $P = 0.012$ ). Intrauterine growth restriction was significantly higher (17% vs. 7%) in ART group ( $P = 0.006$ ). Necrotizing enterocolitis and respiratory distress syndrome were more common in ART group ( $P < 0.001$ ). Hospital stay was longer in ART group ( $P < 0.001$ ). Re-admission, and weight less than 5th percentile were more common after two year in ART group ( $P = 0.021$ ).

**Conclusion:** According to the obtained results, pregnancy after ART has more side effects before and after birth and also in infancy; not only because of multigestation but also due to manipulations in ART.

## Introduction

Assisted reproduction technology (ART) refers to all treatments or procedures that include the in vitro handling of both human oocytes and sperm or of embryos for the purpose of establishing a pregnancy (1). From the birth of the first neonate who was conceived by ART in 1987, significant developments have been yielded in ART and over four million children have been conceived by these techniques (2, 3).

Along with the development of ART, there are more concerns about the safety of these techniques and prognosis of neonates conceived by ART compared to naturally conceived (NC) neonates (2). During ART, various drugs are used to stimulate ovulation, gametogenesis and etc. Moreover, high dose progesterone is used to support luteal phase. All of these techniques can damage gametes or fetus. Intracytoplasmic sperm injection (ICSI) is more aggressive than in vitro fertilisation (IVF), because in ICSI, the sperm is directly injected to the oocyte (4). Moreover, ICSI disable the natural selection of an sperm by oocyte resulting in entering genetically or morphologically abnormal sperms into the oocyte. Besides, transmission of multiple fetus to uterus results in an increased risk of multiple gestation which itself is associated with low birth weight and other maternal of neonatal problems (5, 6).

Despite the recent advances in ART, it may be unseccsesful. Between 1980 and 1985, the rate of a successfule pregnancy by ART was 24% in women less than 40 years age and 14% in women more that 40 years age. Currently, 22.4%, 23.3% and 17.1% of IVF, ICSI and frozen embryo transfer (FET) are successful in Iran, respectively (7). The success rate of ART is dependent to the age of the patient. This success rate is variable from 45% in patient having less than 35 years to 7% in patients having more than 42 years age which is due to the poor response of ovary to stimulation or hyperstimulation syndrome (7).

Different previous studies have investigated the maternal or neonatal outcomes of ART (8-14). These studies have reported various problems in neonates concieved by ART or their mothers including multiple gestation, preterm labor, low birth weight and intra-uterine growth retardation (IUGR). However, none of these studies have reported growth problems in the childs that were concieved by ART.

Although most of the neonates concieved by ART have optimal conditions after labor, investigation of the risk factors of poor outcomes can help planning interventional protocols (8). Hence, The purpose of this study was to determine the two-year prognosis of neonates conceived by ART.

## **Materials And Methods**

### ***Subjects and Design***

A prospective study conducted on neonates concieved by ART betwen April 2017 and October 2019 at Mahdiah Hospital affiliated with Shahid Beheshti University of Medical Sciences in Tehran, Iran. Mahdiah Hospital is a referral and an educational medical hospital with level III neonatal intensive care unit (NICU) and 71 beds of NICU admission, which admits high-risk delivery for pregnant women. Also there are facilities for assisting reproduction technologies.

### ***Data collection***

Data collection was performed by a trained research assistants using a pre-designed check list from the maternal and neonatal medical records. Checklist was including gestational age (GA) at delivery, complications during delivery, demographic characteristics of neonates, hospitalization at ward or NICU, first and fifth minute Apgar score, pre-term labor, IUGR and presence of any disease or anomaly in the neonates. Totally, 165 neonates who were concieved by ART were enrolled in this study. To compare the data of neonates concieved by ART with naturally conceived neonates, 165 NC neonates were enrolled in the study. All neonates were followed two year later to evaluate their weight, hospitalization or mortality. Gestational age  $\leq 37$  weeks was considered premature, and when compared to gestational age, birth weight below the 10<sup>th</sup> or above the 90<sup>th</sup> percentile was considered as small for gestational age (SGA) and large for gestational age (LGA), respectively. Eventually, data of 330 neonates were entered in SPSS.

### ***Statistical Analysis***

Statistical analysis was done with IBM SPSS statistics v 25. We used descriptive and analytical-inferential statistics. To determine the data distribution, One-Sample Kolmogorov-Smirnov Test was used. To analyse the data,  $\chi^2$ , Fisher's exact test, t-test, Mann-whitney test and pearson test were used.

Continuous variables are presented as mean $\pm$ standard deviation. Categorical parameters are expressed as n (%) and were compared using chi-square test. All tests were 2-tailed, and the significance level was set at  $\alpha = 0.05$ .

## Results

IVF was performed in 70.3% of neonates conceived by ART and in the remaining neonates, intrauterine insemination (IUI) was performed. The mean duration of infertility was  $6.8 \pm 4.2$  years. Table 1 shows general characteristics of ART group and NC group. The mean age of mothers in ART group and NC group was not significantly different ( $31.8 \pm 5.9$  v.s  $30.8 \pm 5.5$  years, respectively,  $P = 0.15$ ). The mean gravidity was significantly different between ART group and NC group ( $1.8 \pm 1.2$  v.s  $2.3 \pm 1.3$  respectively,  $P < 0.001$ ). The mean parity was significantly different between ART group and NC group ( $0.4 \pm 0.7$  v.s  $1.0 \pm 0.9$  respectively,  $P < 0.001$ ). Mean gestational age was significantly lower in ART group compared to NC group ( $34.8 \pm 3.6$  v.s  $36.2 \pm 3.0$  respectively,  $P < 0.001$ ). The mean birth weight was significantly lower in ART group compared to NC group ( $2359 \pm 782$  v.s  $2612 \pm 673$  respectively,  $P = 0.002$ ). Moreover, mean gestational age was lower and multiple pregnancy was higher in ART group compared to NC group ( $P < 0.05$ ). Other maternal and neonatal characteristics are depicted in table 1.

Table 2 shows perinatal complications based on mode of conception. Compared to NC group, the prevalence of C/S delivery, Pre-term labor, very low birth weight and low birth weight, maternal pre-eclampsia, need for surfactant and need for mechanical ventilation were significantly higher in ART group ( $P < 0.05$ ). The mean first and fifth minute Apgar score was significantly higher in ART group compared to NC group ( $P < 0.05$ ). While the rate of neonatal hospitalization was similar in both groups, duration of hospitalization was significantly higher in ART group compared to NC group ( $9.2 \pm 7.5$  v.s  $6.2 \pm 6.3$  days respectively,  $P < 0.001$ ).

The results of this study indicate that prematurity is more prevalent in ART group with a peak at GA between 32 and 34 weeks. Indeed, while labor at GA < 32 weeks or 35-36 weeks is more common in NC group, about one third of the neonates in ART group were born at GA between 32 and 34 weeks (table 2). Regarding the prenatal diseases which resulted in neonatal hospitalization, necrotizing enterocolitis (NEC) and respiratory distress syndrome (RDS) were more prevalent in ART group while icter and other diseases were more prevalent in NC group ( $P < 0.05$ ). While the prevalence of prenatal mortality was not different between two groups ( $P = 0.26$ ), intrauterine fetal death (IUFD) and congenital anomaly were only seen in ART group (two cases and one case, respectively).

All neonates were followed two year later. Table 3 shows the outcomes of neonates during two year follow up. Compared to NC group, the hospitalization rate and prevalence of body weight lower than 5%

percentile were higher in ART group at follow up ( $P < 0.05$ ); however, mortality rate was not different between them ( $P = 0.37$ ).

## Discussion

Despite the development of ART techniques, the results of previous studies on the obstetric, perinatal, and neonatal outcomes following ART are not conclusive, partly because of different study designs, populations and countries. The present hospital-based cohort study containing 330 subjects was carried out from April 2016 to October 2017 to investigate pregnancy complications, prenatal and neonatal outcomes related to ART. A 33% increased incidence of multiple gestations in ART pregnancies compared with NC group was found. Compared to the NC group, neonates in ART group were more delivered by a C/S, were more premature with a peak at GA 32-34 weeks, had a higher risk of IUGR, had a lower birth weight, had a higher hospitalization duration and had a higher risk of NEC and RDS. Besides a higher prenatal complications, maternal complications of pregnancy was higher in ART group compared to NC group. A 3-fold increase in incidence of pre-eclampsia in ART pregnancies compared with NC pregnancies was found. Following up the patients for two year showed that infants of ART group are more prone to need to admit at ward and also having a body weight  $< 5\%$  percentile; implying a retarded growth and higher vulnerability to the diseases compared to their NC counterparts.

Previous studies have suggested an increased risk of preterm delivery and IUGR in children conceived by ART (15-18). A recent meta-analysis analyzed data of 27,819 IVF / ICSI pregnancies and found a higher risk of preterm delivery in IVF / ICSI conceived children compared to NC children (18). A prospective cohort study found that the OR for preterm delivery in IVF was 2.19 (95%CI:1.59–3.02) (17). Similarly, the results of the current study showed a higher risk of pre-term delivery especially at GA 32-34 weeks and IUGR. However, some obstetrical or gynecological variables such as multiple gestation may confound the association between ART and pre-term delivery and IUGR suggesting the need for adjusting them in future studies (16).

Besides the pre-term labor, the ART group was more prone to have a low birth weight (LBW) ( $< 2500$  gr) compared to NC group in this study. This result is consistent with previous studies that found an increased risk of LBW among children conceived by ART compared to those conceived without medical assistance (18). Supraphysiological hormonal environment of the IVF cycle may be a significant cause of LBW in ART conception (16). However a Dutch population-based study showed that the birth weight of siblings conceived with IVF was not significantly different from their NC conceived siblings (19). This finding suggests the importance of consideration of maternal infertility as a factor that may contribute to the risk of LBW.

Consistent to our results, previous studies have demonstrated that ART pregnancies are associated with a greater risk of cesarean sections (15, 20, 21). This is not only due to the higher risk of multiple pregnancy in ART, but ART pregnancies were associated with a greater risk of cesarean sections in singleton births (20). Moreover, both elective and emergency cesarean sections are more common among ART

pregnancies (20). However, A population-based Swedish study over a 25 year period showed a gradual decline in this increased risk of cesarean section rate (which nonetheless remains elevated compared to non-IVF pregnancies) implying that development of the ART techniques has resulted a lower risk of C/S (21).

AER appears to be associated with known risks associated with prematurity (22). Our results showed that both RDS and NEC are more prevalent in ART conceived neonates compared to NC neonates. However Turker et al (22) reported that IVF is associated with RDS, but not NEC; similarly, Ahmad et al study showed similar prematurity-related complications for IVF-conceived preterm infants compared to matched controls with the exception of bronchopulmonary dysplasia and respiratory medication exposure (23). The discrepancy between our results and those of Turker et al and Ahmad et al may be related to inclusion of both IVF and IUI conceived neonates in our study, implying the need for investigation of prematurity-related complications in IUI conceived neonates. Moreover, ART and NC group were not matched for prematurity in this study.

Besides prenatal outcomes, ART has adverse obstetric outcomes. In the present study, we found that a 3-fold increase in incidence of pre-eclampsia was associated with pregnancies conceived by ART. Different previous studies have reported a higher risk of pre-eclampsia in ART conceived women (12, 24-26). Pre-eclampsia is a significant cause of maternal and perinatal mortality and morbidity. The mechanisms by which ART leads to pre-eclampsia are not clear yet. Defective placental vascular remodeling is a suggested mechanism of pre-eclampsia (27) so further studies to delineate placental development in ART births are needed to understand the underlying mechanisms.

The main driver for adverse prenatal and obstetric outcomes in ART pregnancies is the higher risk of multiple gestations in ART. Moreover, singleton ART pregnancies still have a higher incidence of adverse outcomes compared to naturally conceived pregnancies (16). Infertility itself and epigenetic changes in genes involved in growth and development during the hormonal stimulation and embryo culture may be independent risk factors (16). The results of this study support previous reports on the association between increased obstetrical and perinatal morbidity and mortality and ART. Also, our findings showed infants of ART group are more prone to need to admit at ward and also having a body weight < 5% percentile; implying a retarded growth and higher vulnerability to the diseases in a two year follow up. It should be noted that based on the previous reports, twins or early preterm neonates conceived via ART compared to non-ART counterparts had similar neonatal outcomes (28, 29) and no additional management may be needed in them.

## Conclusion

This report demonstrates that, ART conceived pregnancies may be accompanied with several side effects. Therefore we recommend for mother with ART conceived pregnancies, to benefit from more vigilant antenatal surveillance and delivery in advanced hospital with tertiary level neonatal intensive care center.

## Tables

**Table 1.** General characteristics of neonates who were conceived by ART (ART group) and naturally conceived neonates (NC group)

Characteristic of neonate	ART group (N=165)	NC group (N=165)	P- value	Odds ratio (CI)
Age of mothers (years)	31.8±5.9	30.8±5.5	0.15	-
Mean gravidity (n)	0.4±0.7	2.3±1.3	<0.001	-
Mean parity (n)	0.4±0.7	1.0±0.9	<0.001	-
Mean gestational age (w)	34.8±3.6	36.2±3.0	<0.001	-
Mean birth weight (gr)	2359±782	2612±673	0.002	-
Sex				
Male (N)	81 (49.4%)	101 (61.6%)	0.03	0.61 (0.39-0.94)
Female (N)	83 (50.6%)	63 (38.4%)		
Previous history of abortion	39 (23.6%)	29 (17.6%)	0.22	1.45 (0.85-2.48)
Nulliparity	120 (72.2%)	64 (38.8%)	<0.001	4.21 (2.65-6.70)
Multiple pregnancy	74 (44.8%)	16 (9.7%)	<0.001	0.33 (0.24-0.72)

**Table 2.** Prenatal outcomes based on mode of conception

Complication		ART group (N=165)	NC group (N=165)	P- value	Odds ratio (CI)
cesarean section		150 (90.9%)	111 (67.3%)	<0.001	0.21 (0.11-0.38)
Prematurity	< 32 w	23 (23.2%)	17 (27%)	<0.05	0.43 (1.56-3.78)
	32-34 w	49 (49.5%)	15 (23.8%)		
	35-36 w	27 (27.3%)	31 (49.2%)		
	Total	99 (60%)	63 (38.2%)		
Mean first minute Apgar score		8.6±1.0	8.4±1.1	<0.05	-
Mean fifth minute Apgar score		9.7±1.0	9.6±0.8	0.01	-
Low birth weight	< 1500 gr	19 (11.5%)	15 (9.1%)	<0.001	-
	1500-2500 gr	81 (49.1%)	39 (23.6%)		
Mean hospitalization duration		9.2±7.5	6.2±6.3	<0.001	-
pre-eclampsia		26 (15.8%)	9 (10.6%)	<0.05	3.24 (1.47-7.16)
PROM		13 (7.9%)	15 (9.1%)	0.84	-
IUFD		2 (1.2%)	0 (0%)	-	-
IUGR		28 (17%)	11 (6.7%)	<0.05	2.86 (1.37-5.96)
Presence of anomaly		1 (0.6%)	0 (0%)	-	-
Need for surfactant		26 (31.7%)	16 (19.5%)	0.11	1.92 (0.94-3.92)
Need for mechanical ventilation		41(50.0%)	34 (41.5%)	0.35	1.41 (0.76-2.62)
Prenatal diseases	RDS	69 (84.1%)	36 (43.9%)	<0.001	-
	NEC	2 (2.4%)	0 (0%)		
	Icter	8 (9.8%)	33 (40.2%)		
	Others	3 (3.7%)	13 (15.9%)		
Prenatal mortality		9 (5.5%)	4 (2.4%)	0.26	-

PROM: Premature rupture of membrane, IUFD: Intrauterine fetal death, IUGR: Intrauterine growth retardation, RDS: Respiratory distress syndrome, NEC: Necrotising enterocolitis



**Table 3.** Infantile outcomes during two year follow up

Outcome	ART group (N=156)	NC group (N=161)	P-value
Ward admission	38 (24.4%)	22 (13.7%)	0.02
Weight < 5% percentile	33 (21.2%)	18 (11.2%)	0.02
Mortality during follow up	3 (1.9%)	1 (0.6%)	0.37

## Abbreviations

assisted reproductive techniques (ART), naturally conceived (NC), Intracytoplasmic sperm injection (ICSI), In vitro fertilisation (IVF), Frozen Embryo Transfer (FET), intra-uterine growth retardation (IUGR), neonatal intensive care unit (NICU), gestational age (GA), small for gestational age (SGA), Intrauterine Insemination (IUI), large for gestational age (LGA), intrauterine fetal death (IUFD), Cesarean section (C/S), Necrotizing enterocolitis (NEC), respiratory distress syndrome (RDS), Low Birth Weight (LBW)

## Declarations

### *Ethics Approval and Consent to Participate*

The present study was extracted from a thesis in pediatrics in Shahid Beheshti University of Medical Sciences. All ethical considerations of the study were approved by the institutional review board and the research ethics committee at Shahid Beheshti University of Medical Sciences, Tehran, Iran (IR.SBMU.NHRC.1397.394). All participants in the study were informed of the study objectives and signed a written informed consent form and were assured of the confidentiality of their personal information and the voluntary nature of participation.

### *Consent for publication:*

Not applicable.

### *Conflict of interest:*

The authors declare that they have no competing interests.

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**Availability of data and materials:** The datasets generated and analyzed during the current study are not publicly available due to exclusively scientific purpose use but are available from the corresponding author on reasonable request.

**Authors' contributions:**

Afjeh and Fallahi (Designing project and supervision), Khoei (data acquisition, drafting the manuscripts in Persian and revising the manuscripts in English), Khoei & Afjeh (data acquisition and revising the manuscripts in English) Tajalli (quality control of data, designing project in statistical analysis section, data analysis and prepare of results), Fallahi, Tajalli, Khoei & Afjeh (Editing and revising the manuscripts in English).

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