

Perinatal Outcomes of Newborn Infants Conceived by Assisted Reproductive Techniques in Royan Institute

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Abstract

Background: The outcomes of such pregnancies have been rarely evaluated in our country. A descriptive study was planned to assess the health and condition of neonates conceived with assisted techniques in a one year period.

Materials and Methods: At Royan Institute, Tehran, 443 women who became pregnant by one of the assisted techniques *in vitro* fertilization (IVF), intrauterine insemination (IUI) and intracytoplasmic sperm injection (ICSI) enrolled in a descriptive study during 16 month period beginning on September, 2007. The sampling method used was non-incidental, consecutive.

Questionnaires regarding the contents of the baby birth card were completed after interviews with the mothers. The time from fertilization of the ovum until delivery was considered as the gestational (conception) age. Pregnant mothers were under periodic evaluation until delivery. Women with stillborn babies were followed via phone contact.

Results: From a total of 443 conceptions, there were 13 (2.9%) pregnancies demised in utero (stillbirths) and 10 (2.6%) who died during the neonatal period. Additionally, 133 (43%) infants were born after multifetal pregnancies and 96 (31%) infants were prematurely born. There were 106 (34.3%) infants with low birth weight (LBW; less than 2500 g), of which 83 (78.3%) LBW infants were multiples. After completion of the study, 71 women were still passing their pregnancy period and no assessed.

Conclusion: The most important factor for untoward perinatal events was multifetal pregnancy. Such pregnancies were more frequently complicated and higher risk. Low birth weight and prematurity were more frequent in singletons conceived by assisted techniques in respect to control singletons.

Keywords: Newborn Infants, Assisted Reproductive Techniques, Prematurity, Low Birth Weight, Multifetal Pregnancy

Introduction

Recent technologic advances have facilitated the fertility of sterile couples. Such interventions come with a high costs. Annually, about one million babies are born by assisted reproductive methods throughout the world. Recently, numerous fertility clinics in our country give infertile couples a chance to become parents. Routine techniques frequently used in Iran are: *in vitro* fertilization (IVF), intrauterine insemination (IUI) and intracytoplasmic sperm injection (ICSI). The outcome of these pregnancies is controversial, according to numerous reports. Prematurity, low birth weight (LBW) and multifetal pregnancies seem to be more frequent in some studies, but others do not confirm this result thoroughly. In many developed countries, about 2 to 4 percent of all infants are born by IVF technique (1). The most important problems following

assisted reproductive techniques are due to multifetal pregnancy, prematurity and LBW. According to studies by Wright and Kissin, 49 to 54% of assisted reproductive techniques (ART) pregnancy products are multifetal (2-5). This rate is significantly higher than normal conceptions (about 3%). Multifetal gestation will bear a higher rate of morbidity and mortality for both mothers and infants. LBW, prematurity, neonatal and congenital malformations as well as sickness are more prevalent among these infants. Bergh, Friedler and Kallen, regarding LBW and neonatal mortality in some Asian and European countries, have reported a four to five-fold increase in IVF neonates as compared with the general population (6-10). The most common impending factor for multifetal gestation in IVF is the transfer of more than one embryo to the uterus. There is a documented direct relationship between preterm la-

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bor and the number of embryos transferred. Whenever the number of embryos are reduced, the rate of preterm deliveries will be reduced (10). The rate of multifetal gestation in one embryo transfer is 0.8% vs. 34.5% in a two embryo transfer (11). Negative maternal factors such as older age, duration and underlying cause of infertility will also have untoward effects on pregnancy outcome. According to reports by Reubinoff and Koivurova, prematurity and LBW are two-fold higher in singleton IVF pregnancies in Belgium and the Netherlands (12-16). Wright et al. recently showed that of all ART singletons in the USA, 9% are LBW and 15% are premature, respectively (5). Wang showed a 2.4 fold higher risk of prematurity and 2.1 fold higher risk of LBW in ART singletons in Australia (17). Reviewing the results of two metaanalyses and 10 case-control studies in IVF/ICSI twins, Helmerhorst et al. reported a 1.07 fold higher risk of prematurity and 1.03 fold higher risk of LBW in IVF twins regarding the control group (18). Mc Donald et al. reviewed 11 studies on IVF and control newborns. Premature births were higher in IVF twins (Odd's ratio 1.57, 95% CI 1.01-2.44) however there was no significant difference in the rate of perinatal mortality and LBW (19). In Pinborg's report from Denmark, there was no significant difference between IVF/ICSI and control twins regarding the incidence of prematurity, LBW and VLBW (20). Bounduelle et al. in a prospective study published in 2002 have shown a higher rate of prematurity in multifetal gestations in the ICSI (54%) vs. IVF (47%) techniques ($p=0.046$). There was a similar incidence of LBW in both groups ($p>0.05$) (21). According to studies by Wennerholm and Loft, prematurity had been reported in 42.3% and 35% of ICSI twins, respectively (22, 23). Go-vaerts reported no difference in the premature birth rate between ICSI and IVF twins (24). Ludwig and Ombelet have shown no significant difference respecting preterm birth and LBW amongst ICSI and IVF singletons (25, 26).

The results of studies on these infants are contradictory. Both artificial conception and laboratory inter-

ventions with zygotes and embryos, can induce variable outcomes. There are no published studies in respect to infants conceived by assisted techniques in our country.

Materials and Methods

There were 443 pregnant women who had been fertilized any one of three assisted techniques (IVF, ICSI, IUI) in Royan Institute, that enrolled in a descriptive study from September 2007 to December 2008. We planned a descriptive study from September 2007 to December 2008. The research Ethics Committee of ACECR and Royan's institutional review board (IRB) approved the study. After ultrasonic confirmation of fetal viability following the 20th week of conception, samples were selected by the non-incident consecutive method. The couples were fully informed about the research study and informed consents were signed by all participants.

All mothers were residents of Tehran and regularly monitored by phone contact. A questionnaire was completed regarding the contents of the birth card. Gestational age was calculated according to the definite time of ovum fertilization. Stillbirths and preterm deliveries were detected by phone contacts. Data were analysed by SPSS-10. T-test and chi-square and t test were used as referral statistical tests.

Results

A total number of 443 mothers whose pregnancy occurred after one of three assisted methods (IVF, ICSI, IUI) enrolled in the study after 20 weeks of gestation. Thirteen pregnancies (2.9%) were terminated by intrauterine fetal demise after the 20th week. From 380 deliveries, 10 newborns (2.6%) died in the neonatal period.

There were 71 newborn infants (18.6%) who were not assessed in our center because of the inability for on-time return, or who were assessed in private clinics.

In our center, 309 (81.4%) newborn infants were assessed, 212 neonates had been conceived by ICSI, 44 by IVF and 53 by IUI methods respectively.

Table 1: Distribution of newborn infants regarding perinatal variables and reproductive techniques

	ICSI	IVF	IUI	Total number
Visited newborns	(68.8%)212	(14.2%)44	(17%) 53	309
Mothers older than 35 years	(22.6%)48	(38.6%)17	(3.7%) 2	(21.7%) 67
Singleton	109 (51.4%)	(72.7%) 32	(66%) 35	(57%) 176
Multifetal	(48.6%) 103	(28.3%) 12	(34%) 18	(43%) 133
Preterm	(31.6%) 67	(43%) 19	(18.8%) 10	(31%) 96
Term & postterm	(69.4%) 145	(57%) 25	(81.2%) 43	(69%) 213
Low birth weight (LBW)	(37.2%) 79	(20.4%) 9	(34%) 18	106 (34.3%)
Appropriate for GA	(62.8%) 133	(79.6%) 35	(66%) 35	(65.7%)203

There were 166 (53.7%) male infants vs. 143 (46.3%) females. The study consisted of 67(21.7%) women who were older than 35 years and 242 (78.3%) who were 35 years or younger. Table 1 has listed the details of the results of the assisted techniques that were used.

From 18 LBW infants who were conceived by IUI, 12 (66.6%) were multifetal gestation products vs. 6 (33.3%) singletons. Of 9 LBW infants conceived by IVF, 6 infants (66.6%) were multiplets vs. 3 (33.3%) singletons. From 79 LBW infants conceived by ICSI, 65 (82.3%) were multiplets vs. 14 (17.7%) singletons.

Discussion

ART began two decades ago in Iran. Women are fertilized at older ages and frequently their conceptions are induced by medical and/or technical remedies. Noxious *ex vivo* conditions, frequent ultrasonic evaluations, hazardous environmental pollutions and smoke cause consecutive abortions and/or neonatal morbidity (27-29).

Appropriately matched control women has been a fundamental limiting factor in such studies. There was no maternal control group in this study. This manner of matching seems impossible in most instances. The rate of stillbirth in our study was 2.9%. According to recent national reports of the Iran Ministry of Health and Medical Education (MOHME) the rate of stillbirth in Tehran is 0.2% (30). 2.6% of all new born infants who died in the neonatal period vs 7.5% MOHME report in Tehran; (30). There were 2.9% vs. 0.2% stillbirths and 2.6% vs. 7.5% neonatal mortality rate, which can be explained by closer supervision and more intense care and/or frequent screening (18, 31-33). In 78% of the cases, women were younger than 35 years. Prompt and relatively easy access to assisted reproductive techniques aids to younger age of clients. There was a 43% rate of multifetal gestation in our study, which is congruent with former studies (49 to 54%) (2-5).

The rate of monozygote twins in the general population worldwide is about 3 to 4 per 1000 pregnancies. According to most studies, the rate of monozygotic twins is significantly higher in ART pregnancies (1.5%) than the general population (34-39). Two possible impending factors are blastocyst culture and chemical or mechanical factors which intervene with the embryonic zona pellucida layer. The rate of multifetal gestation in both IUI and IVF techniques is one from every three pregnancies. In the ICSI method, this rate is 50%. The most implementing factor for multifetal gestation in IVF and ICSI is more than one embryo transfer. In two embryo transfers, 34.5% of pregnancies are multiplets (11). Family preference, older maternal age and high costs of assisted tech-

niques are other causative factors. Preterm delivery is reported in 31% of cases, which is over 4 fold of the general population in Tehran (7.6%) (30). Increased age of the mother, the underlying cause of infertility and multifetal pregnancy may explain the cause. In some studies, the rate of preterm delivery is 4 to 5 fold (6-10) and in others the rate is 2 fold of the general population (12-17). Highest ratio (37.2%) of low birth weight was detected in ICSI infants. Risk ratio for LBW in ICSI was 1.8 fold of IVF infants and former studies reported 1.03 (18). Some investigators did not report a significant difference regarding birth weight between ART infants and normal conception or between ICSI and IVF infants (21, 25, 26). From all low birth weight infants, two thirds were multiplets and one third singletons. After natural multifetal conception, about 7.4% weighed less than 2500 g when born (30).

Conclusion

It seems that most pregnancies induced by assisted reproductive techniques have favorable outcomes in the perinatal period. The most health threatening factor in these infants is multifetal gestation, which can bear a wide range of untoward events throughout pregnancy, at delivery and thereafter in the neonatal period. ART twins have a higher rate of complications such as preterm birth and LBW. The less embryos transferred into uterus, the less frequent perinatal complications. Perinatal problems such as prematurity and LBW are more common in ART singletons in respect to normal conception singletons. According to higher prematurity and LBW rates reported in infants conceived by assisted methods, more extended and multicenter studies can clear the causative factors. The fundamental confounding factor which limits such investigations is the absence of a control group. Hence couples who tolerate different medical and/or surgical interventions, should be matched only with their peers fertilized by a separate technique, not with normally fertilized couples.

Limited sample size and difficult access to this group of infants and their families cause the results less reliable. In the future, selecting a greater number of newborns and implementing them in prospective studies of a longer duration should be considered for better and more reliable results.

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