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Outcome of newborns conceived through artificial reproductive techniques in Tehran Iran

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Abstract

Background: Today there is a rise in the number of newborns conceived by artificial reproductive techniques (ART). Numerous studies have been performed on the perinatal outcome of these pregnancies. However, there is limited data about the condition of health of these newborns in Iran.

Objective: Regarding the higher prevalence of probable complications and symptomatic congenital anomalies, we aimed to determine the state of health of newborns born by ART.

Materials and methods: A total of 109 newborn who were conceived through ART and 479 newborns of spontaneous conception were enrolled into our study.

The study was prospective, case-control study in Tehran, Iran, from March 2003 to March 2004. Both case and control groups were adjusted in regard to race, sex, type of delivery, chronic disease of mother, age of mother, and antenatal steroids administration. All newborns were examined by neonatologist after birth and their outcome were followed until hospital discharge or death.

Data pertaining to clinical and laboratory findings of newborns and death were entered into a questionnaire and subsequently analyzed by appropriate statistical tests. Confidence interval was 95%.

Results : Prematurity, low birth weight (LBW), very low birth weight (VLBW), twins and triplets, small for gestational age (SGA), need for resuscitation at birth, respiratory distress syndrome (RDS) and NICU admission were significantly higher among newborns born after ART than those born through spontaneous conception ($p<0.05$). Regression logistic analysis showed that RDS and NICU admission were more strongly associated with weight at birth and gestational age than with method of conception. However, increased rate of SGA in the case group was associated with multiple pregnancy. Also, there was no significant statistical relationship between the method of conception and the prevalence of congenital anomalies, large for gestational age (LGA), congenital pneumonia, necrotizing entrocolitis (NEC), respiratory air leakage syndromes (ALS), hydrops fetalis, hyperbilirubinemia sepsis, meconium aspiration syndrome (MAS), isseminated intravascular coagulopathy (DIC), cardiac failure, lung hemorrhage, hypoglycemia, hypocalcemia, neutropenia, thrombocytopenia and hemolysis.

Conclusion: Newborns who were conceived by ART were more likely in need of resuscitation at birth regardless of other factors. Furthermore, newborns born after ART were at higher risk of developing prematur birth, LBW, and multiple birth.

Key words: *Assisted reproduction technique, Premature, Prenatal outcome, Congenital malformation*

Introduction

Today, thousands of newborns are born by various artificial or assisted reproductive techniques (ART) worldwide. Many studies have been performed on the method of ART, their success rate, ethical and legal aspects, perinatal outcome (1-5), and the prevalence of congenital anomalies (6-10) but studies on the probable adverse effects and problems associated with these techniques in newborns is scanty (2,11-14). Most of the morbidities experienced in newborns maybe attributed to ART (4-15). On the other hand, in one study it was proposed that most complications were caused by the higher prevalence of prematurity and LBW among these newborns (1,2,5). Wennerholm *et*

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al (6) reported that the only specific malformation which was found to occur in exceed of children born after Intracytoplasmic Sperm Injection (ICSI) was hypospadias (relative risk 3.0) and the increased rate of other congenital malformations was thus mainly a result of a high rate of multiple births. In their study, infants born after ICSI was compared with all naturally conceived newborns in Sweden, immediately after birth and then, they were matched for year of birth, maternal age and multiple pregnancies. In addition, Hansen *et al* (8) showed that infants conceived with the use of ICSI or In Vitro Fertilization (IVF) have twice as high a risk of a major birth defect as naturally conceived infants. Erickson *et al* (9) assessed the presence of congenital malformations in infants in a nation-wide, population-based, case-control study. They showed that an excess of congenital malformations among the case group disappeared when confounders, such as: year of birth, maternal age, parity and period of unwanted childlessness, were taken into consideration. Finally they concluded that the absolute risk for a congenital malformation in association with IVF is small. Dhont *et al* (1) in a survey showed that the prenatal outcome of twin pregnancies obtains with IVF is comparable with that of naturally conceived twins. While, Fitzsimmons *et al* (3) identified that twins obtained with ART have lower perinatal mortality than spontaneously conceived twins. Perinatal and neonatal mortality, gestational age and mean birth weight were not affected in two groups. Ochsenkuhn *et al* (5) reported that in twin pregnancies, the rate of cesarean section and vagianl bleeding and preterm labor were more common after Gamete Intra Fallopian Transfer (GIFT) or IVF, but this difference did not show statistical significance. Assisted reproduction was associated with low birth weight only in twins, when controlled for confounding variables, however perinatal outcome was comparable. One study reported that if ART newborns are compared with matched newborns of normal conception, there will be no difference in regard to their perinatal or neonatal complications (16). Of course, further controlled studies are required to determine whether ART is dangerous for the newborn or not. Problems such as asphyxia, need for resuscitation, hyperbilirubinemia, septicemia, and respiratory, metabolic, endocrine, or hematological disorders were not evaluated. The aim of this study was to determine the clinical and laboratory signs of newborns who were conceived through assisted reproduction in comparison to newborns of spontaneous conception and whether these newborns are faced with more problems during the neonatal period or not.

Materials and methods

This prospective–case control study was performed in one of the public hospitals in Tehran with three levels of neonatal care I (Rooming- inn), II (intermediate neonatal care unit), III (NICU) and a busy delivery unit with around 3500 deliveries per year. Neonates with a gestational age of 25 weeks or more, who were born between March 2003 and March 2004, were enrolled into the study, successively. Cases included all newborns that were born by ART and controls included newborns of spontaneous conception. Cases and controls were matched in respect to race, sex, type of delivery, maternal age, chronic disease of mother and steroid administration prior to delivery. The ratio of cases to controls was around 1:4. A questionnaire consisting of the following information was completed for each child: Mode of conception [normal, Intra uterin insemination (IUI), IVF, GIFT, Zygote intra- fallopian transfers (ZIFT), ICSI, rapid zygote Intra-fallopian transfer (Rapid ZIFT)], number of live twins, maternal age, gestational age, birth weight, chronic disease of mother, prenatal complications (gestational diabetes, pre-eclamsia, eclampsia, placenta praevia, placental abruptio), need for resuscitation at birth, NICU admission, steroid administration prior to birth, final diagnosis at time of hospital discharge or death [including healthy, respiratory distress syndrome, septicemia, hyperbilirubinemia (requiring phototherapy and/or exchange transfusion), pneumothorax, and other any air leak syndromes, meconism aspiration syndromes, necrotizing enterocolitis, lung hemorrhage, hydrops fetalis, prematurity, SGA, LGA], laboratory findings (including leucocytes < 5000/mm^3, platelets < 100000/mm^3, Hb<13mg/dl, reticulocytes>8%, nRBC>10%, lowest blood glucose and highest bilirubin levels during the first week of life, positive culture of sterile body fluids), death or alive, and minor and major symptomatic anomalies based on ICD10.

During the study period, we compared 109 neonates of ART and 479 neonates of spontaneous conception. All neonates were visited by the same Neonatologist. Gestational age ≤ 37 weeks was considered premature, and when compared to gestational age, birth weight below the 10th or above the 90th percentile was considered as SGA and LGA, respectively. Septicemia was defined as a disease,

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which in addition to having clinical signs, involves either positive culture of sterile body fluids or two of the following laboratory findings; leucocytes < 5000/mm^3 or > 25000/mm^3, platelets <100000/mm^3, positive CRP, high ESR and chest radiograph indicating pneumonia. Diagnosis and staging of necrotizing enterocolitis was according to modified Bell's staging (17).

The study was approved by the Medical Ethics Committee of the same hospital and laboratory tests were performed only for neonates with at least one clinical sign or a potential risk factor.

Statistical analysis

Data collected was presented in the form of mean±SD. Using SPSS (V10) software, statistical tests such as, Fisher's exact test, chi-square test, student's t-test, and logistic regression test was used for comparison of the two groups. Confidence interval of 95% was considered as significant.

Results

The lowest and highest birth weights were 600gr and 4450 gr, respectively. Maternal age ranged between 14-48 years and mean maternal age was 29.83±5.05and 28.22±5.22 in the assisted reproduction and spontaneous conception pregnancy group, respectively, both of which lie in the low-risk ages. In the ART neonates group, 17, 4, 68, 4 and 1 were conceived by IVF, GIFT, ZIFT, Rapid ZIFT and ICSI, respectively. The general characteristics of both groups and their comparison based on complications are shown in tables I,II,III. As the tables indicate the following values were significantly higher among the case group than those in the control group: Prematurity (3.56 times), LBW (6.96 times), VLBW (4.006 times), multiple pregnancy (20.17 times), SGA (5.57 times), need for resuscitation at birth (2.56 times), RDS (3.18 times) and NICU admission (6.40 times). Considering only singleton pregnancies in our study, it is seen that the prevalence of prematurity (37% versus 2.9%, odds=2.80, CI= 1.43-5.50, p=0.004) and LBW (29% versus 9.5%, odds= 4.08, CI= 2.19-7.60, p= 0.001) in newborn who were conceived by ART was higher than the control group.

The risk of SGA was 5.5 times higher in newborns conceived through ART (Table II). In order to eliminate the effect of factors including multiple pregnancies, maternal age, race, chronic disease in mother prior to pregnancy and complications of pregnancy such as pregnancy-induced hypertension, two groups were matched and logistic regression test was used for analysis. This analysis showed that multiple pregnancies has more effect on the rate of SGA and that among factors such as pre-eclampsia, eclampsia, multiple pregnancy and method of conception, the only independent factor for prediciting SGA is multiple pregnancy (Table IV).

Table I. General characteristics of newborns who were conceived by ART (case group) and newborns of spontaneous conception (control group)

Characteristics of newborns	Case group	Control group	p- value
Singleton pregnancy (n)	65	463	
Twin pregnancy(n)	26	14	
Multiple pregnancy (n)	18	3	0.001
Boy (n)	65	246	0.23
Girl (n)	44	233	
Mean gestational age (weeks)	37.75(±2.1)	38.80(±1.44)	0.001
Mean weight at birth (gr)	2471(±633)	3020(± 495.5)	0.001
Mean weight at birth of single pregnancy (gr)	2770 (± 560)	3042(± 480)	0.001

n = number

Table II. Perinatal complications based on mode of conception

Characteristics	Case group N(%)	Control group N(%)	p- value	Odds Ratio (CI)
Prematurity	29(26.6)	43(9.2)	0.001	3.56(2.10-6.04)
LBW	60(55)	52(10.9)	0.001	9.96(6.19-16.01)
VLBW	7(6.4)	8(1.7)	0.001	4.006(1.42-11.297)
SGA	31(28.4)	31(6.7)	0.001	5.57(3.20-9.69)
LGA	0(0)	4(0.84)	1	0.9(0.98-0.1)
Need for resuscitation	10(9.2)	18(3.8)	0.018	2.56(1.15-5.72)
NICU admission	12(11)	9(1.9)	0.001	6.40(2.62-15.62)
Prematurity of Single pregnancy	14(21.5)	41(8.8)	0.004	2.80(1.43-5.50)
LBW in single pregnancy	19(29)	43(9.5)	0.001	4.08(2.19-7.60)
Pre- eclampsia	8(7.3)	4(0.84)	0.001	9.32(2.75-30.57)
Multiple births	44(40.3)	17(3.5)	<0.001	20.17(10.77-37.78)

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Table III. Prevalence of diseases based on mode of conception

Disease	Case group N (%)	Control group N(%)	Odds (CI)	p- value
Respiratory distress syndrome	17(15.6)	26(5.5)	3.18(1.66-6.11)	0.001
Septicemia	4(3.7)	16(3.4)	--	NS
Hyperbilirubinemia	7(6.4)	16(3.4)	--	NS
Congenital anomalies	6(5.5)	26(5.5)	--	NS
Pneumonia	0(0)	2(0.4)	--	NS
Respiratory air Leakage syndrome	0(0)	3(0. 6)	--	NS
Meconium aspiration Syndrome	1(0.97)	2(0.4)	--	NS
Hydrops fetalis	0(0)	0(0)	--	NS
Necrotizing enterocolitis	1(0.97)	3(0.6)	--	NS
Disseminated Intravascular coagulopathy	0(0)	1(0.2)	--	NS
Cardiac failure	1(0.97)	5(0.1)		NS

Table IV. Logistic regression results in risk factors

Dependent Variable	Risk factors	*B	**SE	***EXP(β)	P- value	CI(upper – Lower)
SGA	Mode of conception	-0.25	0.40	0.77	0.52	1.713-0.351
	Pre- eclampisa/eclampsia	1.41	0.76	4.13	0.064	18.551-0.921
	Multiple pregnancy	2.86	0.40	17.58	0.001	38.992-7.928
RDS	Mode of conception	0.086	0.40	1.090	0.830	2.38-0.49
	Weight at birth	-0.05	0.097	0.998	0.001	1.15-0.78
	Gestational age	-0.002	0.000	0.998	0.597	0.99-0.99
Need for Resuscitation	Mode of conception	1.228	0.455	0.950	0.007	8.32-1.40
	Gestational age	-0.295	0.136	0.475	0.030	0.971-0.571
	Weight at birth	0.001	0.000	0.001	0.219	1.000-0.002
	Multiple pregnancy	1.195	0.854	3.305	0.162	17.616-0.620
NICU Admission	Mode of conception	0.14	0.632	1.15	0.817	3.997-0.335
	Weight at birth	-0.005	0.001	0.995	0.001	0.997-0.994
	Gestational age	0.046	0.134	1.047	0.732	1.360-0.806

** B=Beta* *** SE=Standard Error* ** * * Exp(B)=Exponential β*

Discussion

Our results showed that around 26% of newborns who were conceived through ART were premature with a lower mean gestational age while this rate was 9% in the group with spontaneous conception. This means that newborns conceived by ART are 3.5 times at higher risk of developing prematurity (Table II). Similar results were obtained by Tallo *et al* in 1995 (11) and Fisch *et al* in 1997 (14), but our results differed from the study performed by Kozinsky in 2003 (16). A meta- analysis performed by Jackson *et al* (18) on 50 similar studies showed that prematurity is significantly higher in the group consisting of newborns conceived by ART. A probable explaniation to this may be the higher rate of multiple pregnancies in these types of pregnancies. However, comparison of singleton pregnancies between two groups in our study showed similar results and prematurity was significantly higher in ART newborns of singleton pregnancies (Table II). Similarly, mean birth weight was lower in the case group and LBW and VLBW rates were significantly higher. After ignoring twin and multiple pregnancies and comparing singleton pregnancies between two groups, results again showed higher values in the ART group. Our findings were in concordance with those of other studies (12, 14, 18-20) but again disagrees with that of Kozinsky *et al* (16).

Another interesting finding was the statistically significant increased rate of SGA in newborns conceived by ART. Similar results were reported in other studies (13,14,16). However, in Jackson *et al*'s study (18) the risk of SGA was1.6 times higher in the ART group but they did not state whether other risk factors associated with SGA were also assessed and whether the case and control groups had been matched in this aspect or not.

The other anticipated result was an increased risk of multiple pregnancies among cases. As reported in other regions of the world, this risk was higher in our study due to multiple embryo transfers and because fetal reduction was not done. The risk of multiple pregnancies was twice as common in neonates in the ART group than this rate in control group. Another study should be performed to compare complications among multiple pregnancies in these two groups.

Furthermore, among the complications of the diseases studied in our survey, resuscitation at birth, NICU admission, and RDS were more common among ART cases. Logistic regression showed that the

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latter two conditions are more strongly related to gestational age and birth weight than on method of conception (Table IV). It seems that newborns who were conceived by ART are not at risk of these complications provided that they have adequate birth weight and full-term gestational age. Need for resuscitation at birth is completely dependent upon the method of conception. In fact, the need for resuscitation at birth is 2.5 times higher among newborns who were conceived by ART as compared to spontaneous conception, when two groups are matched in respect to birth weight, gestational age, and number of fetuses; this had not been pointed out in previous studies.

Other complications like jaundice, pneumonia, septicemia, meconium aspiration syndrome, lung hemorrhage, necrotizing enterocolitis, disseminated intravascular coagulopathy, cardiac failure, congenital anomalies, hypoglycemia, leucopenia, anemia and hemolysis did not differ significantly between the two groups. There are few studies which had assessed these complications. In the study performed by Fish *et al* (1) complications such as jaundice, meconium aspiration syndrome, low Apgar score, asphyxia, hypoglycemia and hypocalcemia were studied and it was seen that jaundice and asphyxia were more common among newborns who were conceived through ART. However, since the case and control groups had not seen matched, definite judgment could not be made in regard to birth weight and gestational age.

In Zuppa *et al*'s study in 2001 (13), twins conceived by ART were compared with twins of spontaneous conception and complications such as low Apgar score, RDS, PDA, septicemia, anemia, IVH and congenital malformations were studied, none of which showed significant difference. In another study performed in 1995 (11) RDS, need for respiratory resuscitation, PDA and septicemia were more frequent in the IVF group but the effect of birth weight and gestational age in these complications were not shown. Finally, our study shows that congenital anomalies occur equally in both groups. However, our results could be more reliable if performed on a larger scale and on more subjects.

Conclusion

Our study showed that the complications which threaten newborns who were conceived through ART include prematurity, LBW, VLBW, SGA, need for resuscitation at birth, NICU admission and RDS (the latter two depend upon gestational age and birth weight). The cause of SGA in these subjects is largely due to the increased risk of multiple pregnancy.

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