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Neonatal mortality and short term prognosis in newborns born after assisted reproduction techniques

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Summary

Aim: With the increase in usage of assisted reproductive techniques (ART) the pregnancy rates complicated with prematurity and multiple gestation show a significant increase. The aim of this study is to evaluate the neonatal mortality, morbidity and short term prognosis in infants born after ART.

Material and Method: One hundred twenty three newborns born after ART and admitted to our Neonatology Clinic between January 1st and December 31st 2007 were included. Hospital records of the patients were evaluated in terms of perinatal and neonatal medical data including congenital anomalies, neonatal mortality and morbidity related to complication of preterm birth such as chronic lung disease, intracranial hemorrhage and retinopathy of prematurity. The control group included 1316 babies of normal pregnancy admitted to our clinic during this period. Statitical analysis was performed using chi-square, Mann-Whitney U and independent-t tests on SPSS 15.0 software.

Results: The study group included 123 ART babies. Rates of prematurity, congenital anomaly and mortality were 95.6%, 8.9 and 20.3%, respectively. Ninety point two percent of the study group showed a history of multiple pregnancy. In comparison with normal pregnancy, ART babies had lower birth weight, higher mortality and higher congenital anomaly rates.

Conclusions: The pregnancies after ART carry higher risk of multiple pregnancy, low birth weight and congenital abnormality which play a role in increased neonatal mortality and morbidity rate. *(Turk Arch Ped 2011; 46: 37-41)*

Key words: Assisted reproduction techniques, neonatal mortality, preterm infant

Introduction

Assisted reproduction techniques (ART) refer to transferring of gametes or embryos into the genital organ of the potential mother by preparing the egg of the potential mother and the sperm of her partner for fertilization using various methods (by providing fertilization outside the body, if necessary). After the birth of the first in vitro fertilization baby in 1978 more than 1 million babies have been reported to be born after ART (1,2). One to three percent of all pregnancies are being reported to be achieved through ART in developed countries (3,4).

With increase in usage of assisted reproduction techniques complications have been reported to increase in both the mother and the baby. The most important complication related to assisted reproduction techniques is multiple pregnancy. Maternal complications associated with multiple pregnancy including preeclampsia, eclampsia, polyhydramnios, premature birth, necessity for urgent Cesarean section, premature membran rupture, cord prolapse, decolman placenta have been reported to increase and consequently maternal mortality and morbidity rates have been reported to be increased (5,6).

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Rates of intrauterine mortality, stillbirth and neonatal mortality are also higher in multiple pregnancies achieved through assisted reproduction techniques (7,8). Risk for premature birth related to multiple pregnancy is increased in these babies. Consequently, complications including bronchopulmonary dysplasia (BPD), respiratory distress syndrome (RDS), retinopathy of prematurity, patent ductus arterious (PDA), septicemia and intracranial hemorrhage are seen more frequently compared to single pregnancies. Increase in the frequency of congenital anomaly in babies born after assisted reproduction techniques is controversial. There are publications reporting that an increase was not shown in the frequency of congenital anomaly compared to the general population, but an increase was found in the babies born after ICSI (Intracytoplasmic sperm injection) (9,10).

The objective of this study was to evaluate neonatal mortality rate and short term prognosis in babies followed up in our clinic who were born after ART pregnancies in comparison with babies born after spontaneous pregnancies.

Material and Method

The study group consisted of 123 newborns born after ART pregnancies and hospitalized between January 1st and December 31st 2007 in Turkish Republic Ministry of Health Izmir Tepecik Education and Researh Hospital Neonatal Clinic. Antenatal and perinatal history, pregnancy age, birth weight, birth height, head circumference, gender, mode of delivery, type of ART used, maternal and paternal age, presence of consanguinity and state of multiple pregnancy were recorded from hospitalization and follow-up files. Presence of congenital anomaly and findings of imaging methods including transfontanel ultrasonography (USG), echocardiography, abdominal USG were recorded. Subjects born earlier than 37 weeks of gestation were considered premature and birth weight lower than the 10th percentile according to gestational week was considered as intrauterine growth retardation. Rates of chronic lung disease, intracranial hemorrhage, retinopathy of prematurity and neonatal mortality were recorded from hospitalization files.

Statistical evaluation

Statistical evaluation was performed between the subjects who died and who survived in the ART babies included in the study group in terms of the above mentioned variants. In addition, statistical comparison was performed between all babies who were born after normal pregnancies and ART babies and between premature babies born after normal pregnancies and premature babies born after ART during the study period in terms of mortality rate, gestational age, birth weight, gender, rate of multiple pregnancy and maternal and paternal age. Statistical analysis was performed using Chi square, Mann-Whitney U and independent-t tests on SPSS 15.0 software.

Results

123 newborn babies who presented to Izmir Tepecik Education and Research Hospital Neonatal Clinic between January 1st and December 31st 2007 and who were born after ART were included in the study group. In the babies included in the study, the type of ART was ICSI in 56 subjects, IVF in 42 subjects and insemination in 25 subjects.

General characteristics of the subjects in the study group are given in Table 1. The study group consisted of 77 male (62.6%) and 46 female (37.3%) subjects. In the study group, mean gestational age was 30.8±2.9 weeks, mean birth weight was 1528.9±563 g, 118 subjects (95.9%) were born premature and 76.9% (98 babies) were born by Cesarean section. Sixty three subjects were born as twin siblings, 48 subjects were born as triplet siblings. Rate of multiple pregnancy was 90.2% and rate of intrauterine growth retardation was 13.8% (17 subjects). Mean maternal age was 30.3±4.7 years, mean paternal age was 34.1±5.4 years and rate of consanguinity was 12.2%.

In the study group, rate of congenital anomaly was found to be 8.9% and mortality rate was found to be 20,3%. Among the subjects with congenital anomaly, four had hypospadias, one had meningomyelocele, one had phocomelia of the left hand, one had macrocephaly, two had microcephaly, one had thoracic deformity and one had VACTERL syndrome. Central nervous system pathology was found in 14 subjects (13.7%) on transfontanel USG. In addition, sensorineural hearing loss was found in 2 subjects and developmental displasia of the hip was found in 6 subjects (6.1%). In 13.8% of the study group, minor cardiac pathologies (foramen ovale, PDA and primum ASD) were found and in 7.3% major cardiac pathology was found. Chronic lung disease was found with a rate of 7% and retinopathy of prematurity was found with a rate of 17.2% in subjects who were born preterm.

Risk factors for mortality in the patients included in the study are compared in Table 2. The mean gestational age was statistically significantly lower in the patients who died compared to the patients who survived ($p<0.001$). Birth

Table 1. General characteristics of the study group

Characteristic	
Gestational age (weeks)	30.8±2.9
Gender (male/female)	77/46
Birth weight (grams)	1528.9±563
Height (cm)	39.7±4.4
Head circumference (cm)	28.6±3.1
Mode of delivery (Normal/cesarean)	25/98
Maternal age (years)	30.3±4.7
Paternal age (yıl)	34.1±5.4
Consanguinity n (%)	15 (%12.2)

weight was 1097±263 grams in the patients who died compared to 1770±561 grams in the patients who survived. Mean height and head circumference were 36.4±2.3 cm and 25.8±1.6 cm, respectively in the patients who died and 40.6±4.4 cm ve 29.3±3.0 cm, respectively in the patients who survived. Statistically significant difference was found between the groups in terms of anthropometric measurements (p<0.001). Rate of Cesarean section was significantly higher in the patients who survived (p<0.001). No significant difference was found between the patients who died and who survived in terms of consanguinity, maternal and paternal age or gender.

When we compared the demographic characteristics of a total of 1316 patients who were born after spontaneous pregnancies and hospitalized in the neonatal clinic at the time of this study and 123 patients who were born after ART pregnancies and followed up at the same time, mean gestational age was found to be statistically significantly lower in the ART group compared to spontaneous pregnancy group (p<0.001). Birth weight was found to be statistically significantly lower in the ART group (p<0.001). In the ART group, rate of male gender, maternal and paternal age and rate of multiple pregnancy were statistically significantly higher (p<0.001). Mortality rate was also found to be statistically significantly higher in the ART group (p<0.005) (Table 3).

The comparison of preterm babies born after spontaneous pregnancies and followed up in our clinic at the time of the study and preterm babies born after ART pregnancies is shown in Table 4. No statistically significant difference was found in terms of gestational age between preterm babies born after spontaneous pregnancies and preterm babies born after ART pregnancies (p=0.17). However, birth weight was significantly lower, maternal and paternal age was found to be significanly older and rate of multiple pregnancy was found to be significantly higher in the ART group. Rate of male gender was found to be significantly higher in preterm babies born after ART compared to preterm babies born after spontaneous pregnancies (p<0.001). Mortality rate was found to be lower in the ART group, but the difference was not statistically significant (p=0.43).

Table 2. Evaluation of mortality rate and risk factors in the study group

	Subjects who survived (n=98)	Subjects who died (n=25)	p
Gestational age (weeks)	31.5±2.6	27.8±2.4	<0.001
Gender (male/female)	61/37	16/9	0.87
Birth weight (grams)	1770±561	1097±263	<0.001
Height (cm)	40.6±4.4	36.4±2.3	<0.001
Head circumference (cm)	29.3±3.0	25.8±1.6	<0.001
Mode of delivery (Normal/cesarean)	10/88	15/10	<0.001
Maternal age (years)	30.1±4.6	31±5.1	0.48
Paternal age (years)	33.9±5.5	34.9±5.2	0.34
Consanguinity n (%)	10 (10.2)	5 (20)	0.18

Table 3. Comparison of babies born after assisted reproduction techniques and babies born after spontaneous pregnancies

	ART group (n=123)	Spontaneous pregnancy group (n=1316)	p
Gestational age (weeks)	30.8± 2.9	35.3±4.8	<0.001
Birth weight (grams)	1528±563	2479±998	<0.001
Gender (male/female)	77/46	504/812	<0.001
Multiple pregnancy	111	184	<0.001
Maternal age (years)	30.3±4.7	27.5±5.6	<0.001
Paternal age (yıl)	34.1±5.4	31±6	<0.001
Number of deaths	25 (20.3)	144 (10.2)	0.005

Discussion

Currently many families have the chance to have children by assisted reproduction techniques. In developed countries, 1-3% of all pregnancies are being reported to be achieved through ART (3,4). There are reports stating that the rate of perinatal problems is higher in pregnancies following assisted reproduction techniques (11-15). In addition to problems related to pregnancy, reports about increased rates of morbidity and mortality in babies born after ART pregnancies have been published.

Jackson et al. (16) reported that the rate of mortality increased 2.9 fold in babies born after ART pregnancies. In studies related to neonatal mortality, ART was reported to

Table 4. Comparison of preterm babies born after assisted reproduction techniques and preterm babies born after spontaneous pregnancies

	Preterm babies born after ART (n=118)	Preterm babies born after spontaneous pregnancies (n=628)	p
Gestational age (weeks)	30.5±2.6	30.9±3.15	0.17
Birth weight (grams)	1461±464	1665±674	0.002
Gender (male/female)	75/43	245/383	<0.001
Multiple pregnancy	109	167	<0.001
Maternal age (years)	30.4±4.7	27.8±5.5	<0.001
Paternal age (years)	34.3±5.3	31.2±5.9	<0.001
Number of deaths	25 (21.1)	113 (18)	0.43

increase the mortality rate in single pregnancies, but no difference was found in twin pregnancies between the ART group and spontaneous pregnancy group in terms of mortality rate (17,18). In our study which compared babies born after ART pregnancies with babies born after spontaneous pregnancies, the mortality rate was found to be higher in the ART group, but no difference was found in preterm babies born after ART pregnancies in terms of mortality rate (p=0.43). This was thought to be related to increased rate of preterm birth and increased rate of small for gestational age babies due to ART. In our study, birth weight was found to be significantly lower in preterm babies born after ART pregnancies compared to preterm babies born after spontaneous pregnancies. This was thought to be related to the increased rate of multiple pregnancy in ART babies.

When ART babies who died and who survived were compared, gestational age and birth weight were found to be factors affecting the mortality rate significantly. In babies born after ART pregnancies, the mortality rate was found to be higher in preterm babies and in babies with lower weight and this was concluded to be related to preterm birth.

One of the most important consequences of ART is increase in multiple pregnancies. In USA, rate of twin pregnancy increased by %59 and rate of triple pregnancy increased by 40.1% compared to 1980 (19). In our study group, 90.2% of 123 subjects (111 subjects) were born after multiple pregnancies. In the study performed by Nayeri et al (20) evaluating 109 ART babies in Iran, rate of multiple pregnancy was reported to be 40.3%. In our study, a higher rate of multiple pregnancy was reported compared to other studies. We believe this is due to the fact that our hospital is a tertiary care regional hospital and more multiple pregnancies requiring intensive care and having more problems related to prematurity are being referred to our clinic.

In our study group, mean maternal age was found to be 30.3±4.7 years. Maternal age has been reported to range between 28 and 34 years in ART pregnancies in other studies performed (21-33). Mean maternal and paternal ages were found to be significantly higher in our study group compared to spontaneous pregnancies. This is thought te be related to infertility time.

One of the most controversial issues in ART pregnancies is the increase in the rate of congenital anomaly in these infants. Generally, the rate of congenital defects is reported to be increased by 30-40% with ART. It is not clear why the rate of congenital anomaly is increased in in vitro fertilization. Deformity of the selected spermatozoon which actually could not fertilize an oocyte has been suggested as a factor. Epigenetic factors have been implicated among other factors. These may lead to anomalies arising from defects related to the infertile couple themselves or arising from the technique of IVF. Tunçbilek et al. (24) reported the rate of congenital anomaly in Turkey to be 3.65%. In our study, the rate of congenital anomaly was found to be 8,9%. In addition, echocardiographic pathologic evidence was found in 21% (26 subjects) of our subjects and major cardiac pathology was found in 7.3% of these subjects (9 subjects). In the study performed by Koivurova et al. (25), congenital cardiac pathology was reported to be observed more frequently in ART babies. However, we believe that the rate of congenital anomaly in our study group could not reflect the actual rate of congenital anomaly in ART babies in our population, since our study subjects required treatment and were referred for medical care.

When diseases related to preterm birth were evaluated in preterm babies in our study group, disorders related to CNS (intracranial hemorrhage and hydrocephalus) were found in 14 subjects (13.7%). Stomberg et al. (26) reported that the frequency of cerebral palsy increased 2.8 fold and the frequency of neurodevelopmental delay increased 4 fold. Since our study subjects were not followed up in the long-term, no interpretation was done in terms of neurodevelopmental delay and neurologic disorders. Since problems related to CNS may be due to preterm or small for gestational age birth, it is thought that long-term multi-center studies are needed.

Sixty two percent of 123 subjects born after ART pregnancies in our study group were male. In the series of Nayeri et al. (20), 59% of 109 ART babies were reported to be male. The rate of male gender was reported to be 52.1% in 3483 IVF/ICS babies in the study performed by Pinborg et al. (27) in Denmark. In our study, gender of ART babies was not found to be related to survival rate. Since our study included babies born after ART pregnancies requiring referral to a neonatology clinic and did not evaluated all ART pregnancies, it did not reflect gender distribution of ART pregnancies in our region or country. However, the fact that neonatal problems including mainly RDS and sepsis are seen more frequently in male babies may be interpreted as higher requirement for neonatal intensive care unit. It is thought that a more comprehensive evaluation on this subject and improvement of the patient record system is needed for our country.

In our study, rates of multiple pregnancy, small for gestational age births and mortality were found to be increased in premature babies born after ART and these were found to be important factors for the prognosis of these babies. In our country where population growth rate is high, increased usage of ART in recent years has led to an increase in multiple pregnancies and premature births. As a result, increased number of babies with problems related to prematurity will cause high workload in neonatal intensive care units which are available in limited number. Consequently, it was concluded that prognosis of babies born after ART pregnancies should be determined and more detailed information should be given to families before using ART.

Conflict of interest. None declared.

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