Türk Pediatri Arşivi
Turkish Archives of Pediatrics

Original Article

Perinatal and somatic growth properties of preterm babies born from spontaneous and *in vitro* fertilization multiple pregnancies

Mehmet Gökhan Ramoğlu[1], Sultan Kavuncuoğlu[2], Sibel Özbek[2], Esin Aldemir[2]

[1]Clinic of Pediatrics, Fatih Sultan Mehmet Training and Research Hospital, İstanbul, Turkey
[2]Clinic of Pediatrics, Kanuni Sultan Süleyman Training and Research Hospital, İstanbul, Turkey

Abstract

Aim: The objective of this study was to examine perinatal and neonatal properties of preterm infants with a corrected age of 24-36 months who were born as a result of spontaneous and *in vitro* fertilization multiple pregnancies, to interrogate somatic growth properties of these infants and evaluate the factors which had an impact by comparing groups.

Material and Methods: A total of 125 children with a birth weight below 2 500 g and a gestational age below the 37th gestational week 60 of whom were born as a result of *in vitro* fertilization multiple pregnancies and 65 of whom were born as a result of spontaneous multiple pregnancies were included in the study. Maternal age and morbidity, early rupture of membranes, birth weigth, gestational week, gender, APGAR score, hospitalization reasons in the neonatal period, requirement for intensive care, frequency of congenital anomaly, outpatient follow-up status, rehospitalization and socioeconomic levels were interrogated in the patients. Detailed physical examination and current height, weight and head circumference measurements were performed and the findings were placed in the growth curves of Neyzi et al. Ethics committee approval was received for this study from the ethics committee of Bakırköy Gynecology Obstetrics and Pediatrics Education and Research Hospital (12.10.2010; no:305).

Results: The rate of cesarean section, mean maternal age, the rate of chronic disease in the mother and the rate of maternal disease which occured during pregnancy were significantly higher in the *in vitro* fertilization group ($p<0.05$). While no difference was found in mean gestational age, birth weight, rate of hospitalization, time of hospitalization, frequency of follow-up in the intensive care unit, rates of congenital anomaly and rehospitalization, APGAR score in the 5th minute was significantly higher in the in vitro fertilization group. The socioeconomical score was not different between the groups, but the in vitro fertilization group presented more regularly for outpatient follow-up visits. Height, head circumference measurements and mean current weight were found to be significantly higher in the in vitro fertilization group ($p<0.05$).

Conclusion: The fact that there was no difference in the rate of hospitalization, time of hospitalization, frequency of follow-up in the intensive care unit, rates of congenital anomaly and rehospitalization was attributed to the fact that the study and control groups were composed of only multiple pregnancies and preterms. (Türk Ped Arş 2014; 49: 17-24)

Key words: Somatic growth, multiple pregnancy, congenital anomaly, preterm, *in vitro* fertilization

Introduction

Presence of more than one fetus in the uterus is called multiple pregnancy. In the last 30 years, the frequency of multiple pregnancy has increased as a result of widespread use of assisted reproduction techniques (ART). In developed countries, multiple pregnancy constitutes 1-3% of all pregnancies. Intrauterine death, stillbirth, preterm delivery and/or low birth weight (LBW) and early neonatal deaths are the most important neonatal problems (1, 2).

The most important reasons of neonatal morbidity and mortality include LBW, preterm delivery and congenital disorders in the whole world (3). The rate of LBW infants is 8.1% in USA (4), 11% in our country according to the Turkey Population and Health Research (5) and 9% according to the study of Kavuncuoğlu et al. (6) in which it was reported that preterm babies constituted 58% of LBW infants. The rate of preterm delivery increases in years and the most important reason of this increase is multiple pregnancies related with ART (7). According to the 2005 report of the National Vital Statistics, the rate of preterm delviery became 12.7% in 2005 in USA by increasing by 2% (8). In our country, this rate was reported to be 5.74% by Altuncu et al. (9) and 5,4% by Kavuncuoğlu et al. (6). Developments in tha area of neonatology and understanding of the physiology of unmatured baby have dramatically contributed to

Address for Correspondence: Mehmet Gökhan Ramoğlu, Clinic of Pediatrics, Fatih Sultan Mehmet Training and Research Hospital, İstanbul, Turkey.
E-mail: mgramoglu@hotmail.com

Received: 27.04.2013 **Accepted:** 21.10.2013

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DOI:10.5152/tpa.2014.1160

an increase in the life span of preterm babies and a decrease in morbidity rates (10, 11). On the other hand, various diseases have been confronted with in the long-term follow-up of very risky preterm babies in years. The main ones among these include neurodevelopmental and somatic growth retardations. While many studies have been conducted on this subject in developed countries, there are limited reports in our country and there is no study related with the follow-up of preterm babies born as a result of spontaneous and in vitro fertilization (IVF) multiple pregnancies. Our aim in this study was to compare the neonatal and prenatal properties of preterm babies born as a result of spontaneous and in vitro fertilization (IVF) multiple pregnancies, to evaluate somatic growth in the 24-36th month and to interrogate prenatal, neonatal and environmental risk factors.

Material and Methods

In our study, preterm babies born before the 37th gestational week with a birth weight below 2 599 g from multiple preganancies between February 2008 and February 2009 in Bakırköy Women's and Children's Education and Research Hospital were evaluated in the corrected 24-36th months in terms of prenatal and somatic growth properties. Spontaneous and IVF multiple pregancies were included in the study. The preterm babies born as a result of IVF were named as the study group and the preterm babies born as a result of spontaneous multiple pregnancies were named as the control group. The study was planned as a cross-sectional, controlled cohort study. Approval was obtained from the ethics committee of the hospital (12.10.2010; number: 305).

Among the properties of the prenatal and neonatal period, mode of fertilization, age of pregnancy, presence of chronic diseases or disease occuring during pregnancy (diabetes, hypertension, preeclampsia, eclampsia), mode of delivery and premature rupture of membranes were questioned and recorded. Rupture of the membranes more than 18 hours before labor was considered premature rupture of membranes (12).

Gender, corrected age, gestational week, birth weight, height, head circumference, APGAR scores in the 1st and 5t^{h} hours, presence of congenital anomaly, histroy of hospitalization and reasons, hospitalization levels (1st, 2nd and 3rd level), hospitalization time, requirement for intensive care, mecahnical ventilation support and/or requirement for surfactant, cranial ultrasonography and magnetic resonance imaging findings in the preterm babies were evaluated and recorded. Last mensturation date and/or new Ballard (13) scoring were used to determine the gestational week. APGAR scores were recorded seperately as the 1st and and 5th minute APGAR scores. The APGAR score in the 1st minute was classified as <4, 4-7, >7 and the APGAR score in the 5th minute was classified as ≤7 and >7.

Suspicious prenatal and perinatal anomalies were defined by pediatric cardiologist, neurologist and radiologist and recorded in the database. In patients in whom cranial and neurodevelopmental pathology was considered, transfontanel ultrasonography was performed using "GE Healthcare LogiqBook XP" ultrasonography device and 8C-RS probe by a pediatric neurologist to investigate hemorrhage and structural anomalies. For a diagnosis of congenital heart disease two-dimensional M-mode and Doppler echocardiographic examination was performed in all newborns by a pediatric cardiologist using "Acuson Cypress" echocardiography device with system number 792US00566 and 7V3C probe. Abdominal ultrasonography was performed using Siemens 5X150 in the patients in whom prenatal suspicious urogenital and gastrointestinal anomaly was present and/or in whom postnatal examination findings were present. Anomalies diagnosed were grouped according to the ICD-10 classification (international disease classification) recommended by the World Health Organization which is used in the whole world (14). This grouping was specified as eye-ear-face-neck, central nervous system, cardiovascular system, cleft palate-lip, gastrointestinal system, genital system, musculoskeletal system and other system disorders.

In the second part of assessment, physical examinations of the patients were performed and somatic growth were evaluated and recorded. The weights of the subjects were measured using Beurer Typ PS 07 ART.Nr:72610 model scale and their heights were measured using "Harpenden Stadiometer". Evaluation of somatic growth was done using height and weight percentile curves prepared for the Turkish children by Neyzi et al. (15). The height, weight and head circumference percentiles of each subjects were calculated according to the corrected age and recorded and the corrected age was calculated using the formula: current age – (40 – gestational week). A value below the 3rd percentile was considered growth failure and a value above the 97th percentile was considered advanced growth. The following points were questioned: need for rehospitalization after discharge, its number and reasons, if a new congenital anomaly was defined, if the subject arrived for follow-up visits and socioeconomical level. In assessment of the socioeconomical level, education levels of the parents, occupations of the parents, number of children, mean monthly income and the properties of the house were questioned and scored.

Statistical analysis

For statistical analyses NCSS (NumberCruncher Statistical System) 2007&PASS 2008 Statistical Software (Utah, USA) program was used. Student's t, Mann Whitney U, Chi-square, Fisher's Exact, Mc-Nemar test and CoehnKappa consistency analysis were used in assessment of the study data. Statistical significance was evaluated with a confidence interval of 95% and at a p value of <0,05.

Results

In our study, 60 IVF subjects who met the study criteria and 65 spontaneous multiple pregnancy cases with similar properties were evaluated. In the spontaneous pregnancy group, there was only a triple pregnancy in addition to twin pregnancies, while one quadruplet and three triple pregnancies were found in the IVF group. 68 of the subjects were female (54.4%) and 57 were male (45.6%). The mean corrected age (24-36 months) at the time of the study was 29.74±2.38 months in the spontaneous group and 27.86±2.81 months in the IVF group. The gestational week was between 26 and 37 weeks according to the Ballard score; the mean gestational week was 34.37±2.28 weeks in the spontaneous group and 33.98±2.62 weeks in the IVF group. 5 subjects (4%) were found to be 28 weeks and younger, 27 subjects (21.6%) were found to be between 28 weeks and 32 weeks and 93 subjects (74.4%) were found to be between 32 weeks and 37 weeks according to gestational week. The mean birth weight (800-2 490 g) was found to be 1 910.15±371.29 g in the spontaneous group

and 1956.66±402.82 g in the IVF group. 4 subjects (3.2%) had a birth weight of 1 000 g and below, 14 subjects (11.2%) had a birth weight between 1001 and 1 500 g and 107 subjects (85.6%) had a birth weight between 1 501 and 2 500 g. When the mode of delivery was examined, it was found that 12 subjects (9.6%) were born by normal spontaneous delivery and 113 subjects (90.4%) were born by cesarean section. Premature rupture of membranes was defined in 7 subjects (5.6%); 6 of these subjects were in the IVF group and one was in the spontaneous pregnancy group.

No difference was found between the groups in terms of gestational week, birth weight and gender (p>0.05), while a significant difference was found in terms of mode of delivery (p<0.01). All subjects in the spontaneous pregnancy group were born by normal spontaneous delivery, while all subjects in the IVF group were born by cesarean section. While the APGAR score in the first minute showed no significant difference between the groups (p>0.05), the APGAR score in the 5th minute was found to be significantly higher in the IVF group (p<0.01). The properties of the subjects by groups are shown in Table 1 and the distribution of APGAR score is summarized in Table 2.

The mean maternal age was 27,80±5,58 years in the spontaneous pregnancy group and 29.80±5.29 years in the IVF group; the mean maternal age, the rate of maternal chronic disease and the rate of occurence of disease during pregnancy were found to be significantly higher in the IVF group (p<0.05).

The hospitalization rate was 61.5% in the spontaneous group and 43% in the IVF group. The mean hospitalization time was 10.62±13.69 days in the spontaneous group and 12.53±16.99 days in the IVF group and the difference was not significant. The most common reason for hospitalization in the ward included respiratory distress, hypoglycemia, hyperbilirubinemia and early sepsis. The rate of hospitalization because of respiratory distress was found to be statistically significantly higher in the IVF group, while no significant difference was found in terms of other reasons of hospitalization. The mean hospitalization time in the intensive care unit was found to be 4.55±11.87 days and 3.12±8.31 days in the spontaneous group and IVF group, respectively. Need for mechanical ventilation was observed in 8 subjects (12.3%) in the spontaneous group and in 2 subjects (3.3%) in the IVF group. Surfactant treatment was performed in 8 subjects (12.3%) in the spontaneous group and in 9 subjects (15%) in the IVF group. No significant difference was found between the groups in terms of hospitalization time in tertiary level intensive care unit, requirement for mechanical ventilation and surfactant treatment (p>0.05) (Table 3).

No significant difference was found between the groups in terms of the frequency of congenital anomaly (p>0.05). While no anomaly was observed in 76.9% of the subjects in the spontaneous pregnancy group at the time of discharge, patent ductus arteriosus (PDA) was found with a rate of 10.8%, atrial septal defect was found with a rate of 3.1%, hypospadias and hydronephrosis was found with a rate of 3.1% and ventricular septal defect+atrial septal defect+PDA and torticollis was found with a rate of 1.5%. No anomaly was observed in 86.7% of the subjects in the study group, while atrial septal defect + PDA was found with a rate of 5%, atrial septal defect and PDA was found with a rate of 3.3% and ventricular septal defect +atrial septal defect was found with a rate of 1.7%. While no new anomaly was found in 118 of the subjects (94.4%), congenital heart anomaly was found in one (0.8%), genitourinary tract anomaly was found in three (4%), gastrointestinal system anomaly was found in two and other anomalies were found in one (0.8%). No significant difference was found between the groups in terms of observation of new anomaly after discharge (p>0.05). Congenital anomalies defined and its distribution by groups are summarized in Table 4.

Table 1. Demographic properties of the patients by groups

		Spontaneous pregnancy group Mean±Standard Deviation	IVF group Mean± Standard Deviation	$^{+}$p
Corrected age(months)		29.74±2.38	27.86±2.81	0.001**
Gestational week		34.37±2.28	33.98±2.62	0.381
Birth weight (g)		1910.15±371.29	1956.66±402.82	0.503
		n (%)	n (%)	$^{++}$p
Gender	Female	36 (55.4)	32 (53.3)	0.818
	Male	29 (44.6)	28 (46.7)	
Mode of delivery	NKD*	12 (18.5)	0 (0)	0.001**
	C/S*	53 (81.5)	60 (100)	
Gestational week	≤28	2 (3.1)	3 (5)	0.858
	28-32	14 (21.5)	13 (21.7)	
	32-37	49 (75.4)	44 (73.3)	
Birth weight	≤1.000	1 (1.5)	3 (5)	0.068
	1.000-1.500	11 (16.9)	3 (5)	
	1.500-2.500	53 (81.5)	54 (90)	

$^{+}$Student's t test, $^{++}$chi-square test, •Fisher's Exact chi-square test, **p<0.01

*NSD: normal spontaneous delivery; *C/S: cesarean section; IVF: *in vitro* fertilization

Table 2. Distribution of APGAR scores by groups

	Spontaneous pregnancy group Mean±Standard Deviation (Median)	IVF group Mean±Standard Deviation (Median)	+p
Apgar 1st minute	5.58±1.31 (6)	5.68±1.29 (5)	0.709
Apgar 5th minute	8.37±0.80 (9)	8.73±0.73 (9)	0.005*
	n (%)	n (%)	
Apgar 1st minute	<4	4 (6.2)	4 (6.7)
	4-7	60 (92.3)	54 (90)
	≥8	1 (1.5)	2 (3.3)
Apgar 5th minute	≤7	55 (84.6)	56 (93.3)
	>7	10 (15.4)	4 (6.7)

Mann-Whitney U test; IVF: *in vitro* fertilization; *p<0.01

Table 3. Distribution of hospitalization charactersitics in the neonatal period by groups

		Spontaneous pregnancy group Mean±Standard Deviation	IVF group Mean±Standard Deviation	+p
Hospitalization time (days)		10.62±13.69	12.53±16.99	0.464
		n (%)	n (%)	++p
Stay in the ward	Hospitalized	40 (61.5)	43 (71.7)	0.231
	Non-nospitalized	25 (38.5)	17 (28.3)	
Hospitalization	1st level	2 (5)	6 (14.0)	0.260
(n=83)	2nd level	23 (57.5)	26 (60.5)	
	3rd level	15 (37.5)	11 (25.6)	
Reasons of hospitalization in the ward	Respiratory distress	31 (77.5)	19 (44.2)	0.002**
	Hypoglycemia	13 (32.5)	12 (27.9)	0.649
	•Polysthemia	2 (5)	4 (9.3)	0.677
	•Hyperbilirubinemia	11 (27.5)	9 (20.9)	0.609
	Early sepsis	8 (20)	8 (18.6)	0.872
	•PROM*	0 (0)	2 (4.7)	0.495
	Other	7 (17.5)	4 (9.3)	0.271

+Mann-Whitney U test; ++chi-square test; •Fisher's Exact Chi-square test; *p<0.05; **p<0.01; *PROM: premature rupture of membranes; IVF: *in vitro* fertilization

Rehospitalization was needed in 46 of the subjects (36.8%). When the number was examined in terms rehospitalization, it was found that 29 subjects experienced one rehospitalization, 13 subjects experienced two rehospitalizations and 4 subjects experienced more than three rehospitalizations. The most common hospitalization reason was lower respiratory tract infection (46.8%) and hyperbilirubinemi (36.2%) followed this. No difference could be found between the groups in terms of hospitalization state, number and reasons (p>0.05) (Table 5). While no significant difference was found between the groups in terms of socioeconomical level scores (p>0.05), a statistically highly significant difference was found in terms of arrival rates for follow-up visits (p<0.01). The rate of regular follow-up visits was 33.8% in the spontaneous pregnancy group and 61.7% in the IVF group.

Since a statistically significant difference was found between the gorups in terms of corrected age, a subgroups including 27-33 months was selected based on the distribution on the bell curve of the subjects according to corrected age in order to evaluate the somatic growth properties of the subjects. This group included 91 subjects 35 of whom were in the IVF group and 56 of whom were in the spontaneous pregnancy group (Table 6). The head circumference ranged between 44.5 cm and 52 cm; the highest distribution was observed between the 10th and 25th percentile and between the 75th and 90th percentile in the IVF group, while it was intensified in the 10-25th percentile in the spontaneous pregnancy group. In the spontaneous pregnancy group, the current weight and height values were also found to be below the 3rd percentile in two subjects in whom the head circumference was below the 3rd percentile. One of these subjects was born in

the 31st gestational week and the other one was born in the 36th gestational age. They were both "small for gestational age (SGA)" babies. The subject who had a head circumference below the 3rd percentile in the spontaneous pregnancy group was excessively LBW and excessively preterm baby. In two subjects who had a head circumference above the 90th percentile, there was no history of intracranial hemorrhage, meningitis or hydrocephalus. Familial macrocephaly was considered in these subjects who were found to have normal neurological assessment and it was planned to continue to follow up these subjects.

The current weight measurements ranged between 8.2 and 18.5 kg. The current weight measurements in the study group were found to be significantly higher in the study group compared to the spontaneous pregnancy group. While the distribution was between the 25th and 50th percentile and between the 50th and 75th percentile in the spontaneous pregnancy group, it was intensified in the 50-75th percentile in the IVF group. In the spontaneous pregnancy group, there were three subjects with a weight below the 3rd percentile. In the IVF group, there was one subject with a weight below the 3rd percentile. In the spontaneous pregnancy group, height and head circumference measurements were also below the 3rd percentile in two of three subjects (they had symmetrical growth failure [symmetrical SGA]). One of these subjects was excessively preterm baby and the other one was moderately preterm baby. In the spontaneous pregnancy group, the head circumference and height measurements of the third subject were above the 3rd percentile and this subject had a history of three rehospitalizations after discharge. The subject in the IVF group was excessively LBW and excessively preterm baby and this subject had a history of three rehospitalizations after discharge.

The heiaght measurements ranged between 80 and 99 cm. The height measurements of the study group were found to be statistically significantly higher in the study group compared to the spontaneous pregnancy group ($p<0.05$). While there were two subjects with a height measurement below the 3rd percentile in the spontaneous pregnancy group, all subjects in the IVF group had a height measurement above the 3rd percentile. These two subjects in the spontaneous pregnancy group were preterm babies with height, weight and head circumference measurements below the 3rd percentile.

Table 4. Distribution of congenital anomaly by groups

	Spontaneous pregnancy group n (%)		IVF group n (%)	
No	46 (70.8)		49 (81.7)	
Yes	19 (29.2)		11 (18.4)	
	Spontaneous		IVF	
	n	%	n	%
Congenital heart disease	10	15.3	9	15
Gastrointestinal system	2	3.1	0	0
Genitourinary system	5	7.7	2	8.3
Other	2	3.1	0	0

IVF: *in vitro* fertilization

Discussion

In our study, prenatal, perinatal and postnatal properties and socioeconomical levels of preterm babies born as a result of IVF and spontaneous multiple pregnancy were examined in detail; hospitalization numbers, reasons for hospitalization, somatic growth and demographic properties of 60 preterms babies in the IVF group and 65 preterm babies in the spontaneous pregnancy group were evaluated in the 24-36th months.

When the maternal properties were examined, the mean maternal age was found to be significantly higher in the IVF group compared to the spontaneous pregnancy group ($p<0.05$). Pinborg et al. (16), Güney et al. (17), Manoura et al. (18) and Tallo et al. (19) reported that the

Table 5. Evaluation of the groups in terms of hospitalization variables

		Spontaneous pregnancy group n (%)	IVF group n (%)	p
Rate of hospitalization		26 (40)	20 (33.3)	0.440
Number of hospitalizations	1	16 (61.5)	13 (65)	0.894
	2	8 (30.8)	5 (25)	
	≥3	2 (7.7)	2 (10)	
Reasons of hospitalization	Hyperbilirubinemia	10 (37)	7 (35)	0.866
	LRTI*	11 (40.7)	11 (55)	0.333
	•AGE/Fluid loss*	0 (0)	1 (5)	0.426
	•UTI*	1 (3.7)	0 (0)	1.000
	Other	9 (33.3)	3 (15)	0.154

Chi-square test; •Fisher's Exact Chi-square test; *LRTI: lower respiratory tract infection; *AGE: acute gastroenteritis; *UTI: urinary tract infection; IVF: *in vitro* fertilization

Table 6. Comparison of the groups in terms of somatic growth properties

	Spontaneous pregnancy group n (56) Mean±Standard Deviation	IVF group n (35) Mean±Standard Deviation	p
Corrected age (months)	30.11±1.71	29.4±1.73	0.06
Gestational week	34.34±2.24	33.54±3.14	0.16
Birth weight (g)	1910.89±368.43	1938.29±489.15	0.77
Had circumference (cm)	47.91±1.45	49.10±1.31	0.001*
Weigth (kg)	12.75±1.74	13.58±1.60	0.025*
Height (cm)	90.36±3.95	93.2±3.87	0.001*

Student's t test; IVF: *in vitro* fertilization

mean age was higher the women who became pregnant by way of ART compared to the mean age of the spontaneous pregnancy group.

In our study, the rate of occurence of disease in the mother was found to be significantly higher in the IVF group similar to the study of Tallo et al. (19) ($p<0.05$). In contrast, no difference could be found between the two groups in terms of the rate of occurence of disease in the mother (17, 20).

In the literature, cesarean rates of IVF pregnancies have been reported to be high (16, 17, 21) and this has been related with the fact that IVF babies are precious, families have high expectations and a high level of anxiety disorder (18). In our study, the rate of cesarean section was found to be 100% in the IVF group and 18.4% in the spontaneous pregnancy group.

It was observed that the mean gestational week in the IVF group was lower compared to the spontaneous pregnancy group. Similarly, Pinborg et al. (16), Güney et al. (17) and Brandes et al. (22) reported that the mean gestational week in IVF twins was lower compared to spontaneous pregnancy twins.

In our country, Güney et al. (17) seperated APGAR scores as below 4 in the 1rst minute and below 7 in the 5th minute and reported that the APGAR scores in the 5th minute were significantly higher in the IVF group. Ochsenkhün et al. (23) compared the babies born by way of ART and by spontaneous pregnancy and found no significant difference between the groups in terms of the APGAR score in the 1st, 5th and 10th minute and umbilical artery pH. Moise et al. (24) and Koudstaal et al. (20) performed a study including similar groups and found no significant difference in terms of the APGAR score in the 5th minute. In our study, the APGAR score in the 1st minute was 5.58±1.31 in the spontaneous pregnancy group and 5.68±1.29 in the IVF group ($p=0.709$) and the APGAR score in the 5th minute was 8.37±0.80 in the spontaneous pregnancy group and 8.73±0.73 in the IVG group ($p=0.005$); the APGAR score was significantly lower in the spontaneous pregnancy group.

When hospitalization properties were compared, no significant difference was found in terms of rates of hospitalization in the ward, hospitalization levels, hospitalization times and follow-up times in the tertiery level neonatal intensive care unit. These results were similar to the results of Moise et al. (24). In both groups, the main reasons of hospitalization included respiratory distress, hypoglycemia, hyperbilirubinemia and sepsis and there was no difference in terms of hospitalization times. The rates of hospitalization because of respiratory distress and mechanical ventilation support were found to be higher in the IVF group.

Baxi et al. (21) and Moise et al. (24) reported that the frequency and time of hospitalization in the hospital and/or in the intensive care unit was significantly higher and longer in the IVF group. In 2009, Hansen et al. (25) reported that IVF twins were followed up in the intensive care unit with a higher rate compared to spontaneous pregnancy twins, while Güney et al. (17) found no difference between the IVF group and the spontaneous pregnancy group in terms of the frequency of hospitalization in the intensive care unit similar to our study. It was thought that the fact that no difference was found in terms of the rates of hospitalization in the hospital and in the intensive care unit, hospitalization time and the frequency of mechanical ventilation-surfactant treatment in our study was related with inclusion of only preterm babies born from multiple pregnancies and with the high mean gestational week and the high mean birth weight.

In some studies it has been reported that ART in infertility treatment leads to an increase in the frequency of congenital anomaly (26, 27), while no significant difference has been reported in terms of congenital anomaly between the groups in studies comparing ART and spontaneous pregnancies performed by different centers at different times (16, 28, 29). In the literature, there are publications reporting increased important delivery problems (30), cardiac disorder (31), male urogenital system disorders and hypospadias in IVF children (32, 33). In the study performed by Güney et al. (17) in our country, no significant difference was found between the spontaneous pregnancy group and the IVF group in terms of the frequency of congenital anomaly. In our study, differences in the distribution of congenital anomaly were observed, although there was no significant difference in the frequency of congenital anomaly in the neonatal period and after discharge. In our study, all genitourinary system anomalies found in the neonatal period were in the spontaneous pregnancy group. Ten subjects with cardiac anomaly 7 of whom had PDA alone were found in the spontaneous pregnancy group and a total of 8 subjects two of whom had PDA alone were found in the IVF group. In both groups, cardiovascular system anomalies were found with the highest rate and this was followed by genitourinary tract anomalies.

In our study the rate of hospitalization in the subjects was found to be 46/125 (36.8%). The most common reasons included lower respiratory tract infection (46.8%) and hyperbilirubinemia (36.8%). No significant difference was found between the groups in terms of need for hospitalization, number of hospitalization and reasons of hospitalization (p>0.05). In the literature, the largest studies investigating the need for hospitalization in the early childhood period in spontaneous pregnancy and ART children have been reported from Sweden, Denmark and Finland (31, 34, 35). In Finland, 4559 IVF babies (single-multiple) born between 1996 and 1999 were followed up until the age of four and the frequency of presentation to hospital and hospitalization time were found to be significantly higher in IVF single pregnancies compared to spontaneous single pregnancies (33). On the other hand, no difference was found in multiple pregnancies which was compatible with the studies performed by Pinborg et al. (34) and Koivurova et al. (31). Ericson et al. (35) found the rates of hospitalization in IVF children to be higher in both the single and multiple groups compared to the control group. In our study, the fact that no difference was found between the groups in terms of hospitalization rates, numbers of hospitalization and reasons of hospitalization was related with the small number of subjects included in the study and with the fact that the groups were composed of LBW preterm babies born from multiple pregnancies.

33.8% of the spontaneous pregnancy group and 61.7% of the IVF group were brought to outpatient follow-up visits regularly. While no significant difference was found between the two groups in terms of socioeconomical level score, the fact that the rate of presentation for follow-up visits was significantly higher in the IVF group compared to the sponatenous pregnancy group İVF (p<0.01) shows that children born as a result of ART are viewed as "precious baby" also by their families. In the literature, no difference was found between the ART and spontaneous pregnancy groups in terms of socioeconomical level in the study performed by Pinborg et al. (34). The fact that no difference was found in terms of the mean socioeconomical level score was related with the fact that assisted reproduction techniques in our country are compensated by social security.

While the mean head circumference measurement in the study group (49.1±1.31 cm) was found to be significantly higher compared to the spontaneous pregnancy group (47.91±1.45 cm) (p<0.01), 2 subjects with a head circumference below the 3rd percentile were defined in the spontaneous pregnancy group. The mean weight and height measurements were found to be 13.07±1.73 kg and 91.46±4.14 cm, respectively. The mean weight and height measurements in the study group were found to be significantly higher (p<0.05). Three subjects in the spontaneous pregnancy group and one subject in the study group had a head circumference below the 3rd percentile. While all subjects in the study group had a height within the normal limits, two subjects in the spontaneous pregnancy group had a height measurement below the 3rd percentile. In the spontaneous pregnancy group, the weight, height and head circumference were below the 3rd percentile in two of our subjects. These subjects had symmetrical growth failure (symmetrical SGA). When the etiology of the subject who had a head circumference above the 90th percentile in the IVF group and the etiology of the other subject in the spontaneous pregnancy group were examined, it was learned that none of the subjects had a history of intracranial hemorrhage, meningitis and hydrocephaly. Since the assessment made by a pediatric neurologist and present imagings were found to be normal, these subjects were evaluated to have familial macrocephaly.

Somatic growth is under influence of genetic and environmental factors starting from the intrauterine period. Although many studies examining the growth of babies born as a result of ARTs have been performed, the results are confusing. In most of the studies, multiple pregnancies, SGA and preterm babies have been included in comparisons. This is not surprising considering that ART is one of the most important reasons of multiple pregnancy (36). Koivurova et al. (37) compared 299 IVF babies with 558 children born as a result of spontaneous pregnancy without discriminating single-multiple pregnancies and evaluated 150 IVF and 280 spontaneous single pregnancy and 100 IVF and 100 spontaneous twins (the last evaluation was made at the age of three years). In this evaluation, the children in the IVF group were found to be shorter and lighter compared to the spontaneous pregnancy group for the group for which no discrimination was made for single-multiple pregnancy. In the study group in which single pregnancies were compared, the height was found to be similar in both groups, while the weight was found to be lower in the IVF group compared to spontaneous pregnancy group. In the group where twin pregnancies were compared, height and weight properties were found to be similar for both groups. Brandes et al.. (22) and Saunders et al. (38) reported that there was no difference in terms of weight, height and head circumference measurements in IVF and spontaneous pregnancy subjects evaluated at about 2 years.

Since IVF groups also include SGA and preterm babies in most studiest, the IVF group is expected to be shorter and lighter compared to the spontaneous pregnancy group (36). On the other hand, different results have been obtained in some studies conducted in recent years. In 2009, Makhoul et al. (39) noted that the children aged 6-10 years in the IVF group were taller compared to the spontaneous pregnancy group. In the study performed by Miles et al. (40) in which children born from IVF and spontaneous single pregnancies were evaluated in the adolescence period, the mean height of the children in the IVF group was found to be higher compared to the spontaneous pregnancy group. Again in the same study, serum IGF-I and IGF-II levels were found to be higher in the IVF group. In our study, the mean values of current weight, height and head circumference measurements were significantly higher in the IVF group compared to the spontaneous pregnancy group (p=0,025), (p=0,001), (p=0,001).

In our study, the mean value of current weight, height and head circumference measurements in the IVF group was found to be significantly higher compared to the spontaneous pregnancy group (p<0.05). The rate of cesarean section, the mean maternal age, the rate of chronic disease in the mother, the rates of morbidity during pregancy and the frequency of presentation for outpatient visits were found to be significantly higher in the IVF group. No significant difference was found between the two groups in terms of socioeconomical level, hospitalization time in the hospital and intensive care unit and intensive care requirements.

There are many studies conducted on this subject in the literature. Similar results have been obtained in some of these studies, while some others have reported different results. Methodological weakness and confusing factors are present in most of the studies conducted to evaluate growth of children born by way of

assisted reproduction techniques. We think that studies which include a higher number of subjects and in which groups are matched fully are needed to confirm these results.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Bakırköy Gynecology Obstetrics and Pediatrics Education and Research Hospital (12.10.2010; no:305).

Informed Consent: Written informed consent was obtained from patients' parents who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - M.G.R., S.K.; Design - M.G.R., S.K.; Supervision - M.G.R., S.K.; Materials - M.G.R., S.K., S.Ö., E.A.; Data Collection and/or Processing - M.G.R., S.K., S.Ö., E.A.; Analysis and/or Interpretation - M.G.R., S.K.; Literature Review - M.G.R., S.K.; Writer - M.G.R., S.K.; Critical Review - M.G.R., S.K.; Other - M.G.R., S.K., S.Ö., A.E.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

References

1. Assisted reproductive technologies. In: Speroff L, Fritz MA (eds). Clinical gynecologic endocrinology and infertility. 7th edition. Philadelphia: Lippincott Williams, 2005; 32: 1215-74.
2. Van Voorhis BJ, Stovall DW. Autoantibodies and infertility: a review of the literature. J Reprod Immunol 1997; 33: 239-56.
3. Stoll BJ, Chapman IA. The high risk infant. In: Kliegman R, Behrman R, Jenson H, (eds). Nelson textbook of pediatrics. 18.th edition. USA: Saunders, 2007: 698-711.
4. Mathews TJ, MacDorman MF. Infant mortality statistics from the 2007 period linked birth/infant death data set. Natl Vital Stat Rep 2011; 59: 1-25.
5. Türkiye Nüfus ve Sağlık Araştırması-2003. Hacettepe Üniversitesi Nüfus Etütleri Enstitüsü, 2004.
6. Kavuncuoğlu S, Altuncu E, Ramoğlu M, ve ark. Ünitemizde bir yıl içinde doğan tüm yenidoğanların demografik dağılımı, mortalite ve morbidite sonuçları. JOPP 2010; 2: 106-14.
7. Macones AG. Prematurity. Prevention and causes. In: Taeusch HW, Ballard RA, Gleason CA, (eds). Avery's disease of the newborn. 8th edition. Philadelphia: Elsevier Saunders, 2005: 139-46.
8. Martin JA, Hamilton BE, Ventura SJ. Births: final data for 2005. Natl Vital Stat Rep 2007; 56: 1-30.
9. Altuncu E, Kavuncuoğlu S, Gökmirza PÖ, Albayrak Z, Arduç A. The incidence of low birth weight in 5000 liveborn infants and the etiology of fetal risk factors. MMJ 2006; 19: 46-51.
10. Eichenwad EC. Care of extremely low-birtweight infant. In: Taeusch HW, Ballard RA, Gleason CA, (eds). Avery's disease of the newborn. 8th edition. Philadelphia: Elsevier Saunders 2005: 410-26.
11. Greenough A, Dimitriou G, Prendergast M, Milner AD. Synchronized mechanical ventilation for respiratory support in newborn infants. Cochrane Database Syst Rev 2008; 1: CD000456.
12. Marsal K, Herbst A. Time between membrane rupture and delivery and septicemia in term neonates. Obstet Gynecol 2007; 110: 612-8.
13. Ballard JL, Khoury JC, Wedig K, Wang L, Eilers-Walsman BL, Lipp R. New Ballard score, expanded to include extremely premature infants. J Pediatr 1991; 119: 417-23.
14. International statistical classification of diseases and related health problems. 10th edition. Revision volume 2. Instruction manual 2010 Edition, World Health Organisation.
15. Neyzi O, Saka H, Kurtoğlu S. History of anthropometric studies in Turkish children. Türkiye Klinikleri J Pediatr Sci 2012; 8: 1-13.
16. Pinborg A, Loft A, Rasmussen S, et al. Neonatal outcome in a Danish national cohort of 3438 IVF/ICSI and 10362 non IVF/ICSI twins born between 1995 and 2000. Human Reprod 2004; 19: 435-41.
17. Güney M, Oral B, Mungan T, Özbasar D. İn vitro fertilizasyon sonrası ikiz gebeliklerin antepartum, intrapartum ve perinatal sonuçları. J Turkish-German Gynecol Assoc 2006; 7: 115-9.
18. Manoura A, Korakaki E, Hatzidaki E, Bikouvarakis S, Papageorgiou M, Giannakopoulou C. Perinatal outcome of twin pregnancies after in vitro fertilization. Acta Obstet Gynecol Scand 2004; 83: 1079-84.
19. Tallo CP, Vohr B, Oh W, Rubin LP, Seifer DB, Haning RV. Maternal and neonatal morbidity associated with in vitro fertilization. J Pediatr 1995; 127: 794-800.
20. Koudstaal J, Bruinse HW, Helmerhorst FM, Vermeiden JPW, Willemsen WNP, Viser GHA. Obstetric outcome of twin pregnancies after in-vitro fertilization: a matched control study in four Dutch University hospitals. Hum Reprod 2000; 15: 935-40.
21. Baxi A, Kaushal M. Outcome of twin pregnancies conceived after assisted reproductive techniques. J Hum Reprod Sci 2008; 1: 25-8.
22. Brandes JM, Scher A, Itzkovits J, Sarid M, Thaler I, Gershoni-Baruch R. Growth and development of children conceived by in vitro fertilization. Pediatrics 1992; 90: 424-9.
23. Ochsenkühn R, Strowitzki T, Gurtner M, et al. Pregnancy complications, obstetric risks, and neonatal outcome in singleton and twin pregnancies after GIFT and IVF. Arch Gynecol Obstet 2003; 268: 256-61.
24. Moise J, Laor A, Armon Y, Gur I, Gale R. The outcome of twin pregnancies after IVF. Hum Reprod 1998; 13: 1702-5.
25. Hansen M, Colvin L, Petterson B, Kurinczuk J, Klerk N, Bower C. Twins born following assisted reproductive technology: perinatal outcome and admission to hospital. Hum Reprod 2009; 24: 2321-31.
26. Merlob P, Sapir O, Sulkes J, Fisch B. The prevalence of major congenital malformations during two periods of time, 1986-1994 and 1995-2002 in newborns conceived by assisted reproduction technology. Eur J Med Genet 2005; 48: 5-11.
27. Hansen M, Bower C, Milne E, Klerk N, Kurinczuk J. Assisted reproductive technologies and the risk of birth defects-a systematic review. Hum Reprod 2005; 20: 328-38.
28. Aboulghar MA. Perinatal complications of assisted reproduction. Croat Med J 2005; 46: 751-8.
29. Bonduelle M, Legein J, Derde MP, et al. Comperative follow-up study of 130 children born after intracytoplasmic sperm injection and 130 children born after in-vitro fertilization. Hum Reprod 1995;10: 3327-31.
30. Olson CK, Keppler-Noreuil KM, Romitti PA, et al. In vitro fertilization is associated with an increase in major birth defects. Fertil Steril 2005; 84: 1308-15.
31. Koivurova S, Hartikainen AL, Gissler M, Hemminki E, Sovio U, Jarvelin MR. Neonatal outcome and congenital malformations in children born after in-vitro fertilization. Hum Reprod 2002; 17: 1391-8.
32. Klemetti R, Gissler M, Sevon T, Koivurova S, Ritvanen A, Hemminki E. Children born after assisted fertilization have an increased rate of major congenital anomalies. Fertil Steril 2005; 84: 1300-7.
33. Klemetti R, Sevon T, Gissler M, Hemminki E. Health of children born as a result of in vitro fertilization. Pediatrics 2006; 118: 1819-27.
34. Pinborg A, Loft A, Rasmussen S, Andersen AN. Hospital care utilization of IVF/ICSI twins followed until 2–7 years of age: a controlled Danish national cohort study. Hum Reprod 2004; 19: 2529-36.
35. Ericson A, Nygren KG, Olausson PO, Kallen B. Hospital care utilization of infants born after IVF. Hum Reprod 2002; 17: 929-32.
36. Savage T, Peek J, Hofman PL, Cutfield WS. Childhood outcomes of assisted reproductive technology. Human Reprod 2011; 26: 2392-400.
37. Koivurova S, Hartikainen AL, Sovio U, Gissler M, Hemminki E, Jarvelin MR. Growth, psychomotor development and morbidity up to 3 years of age in children born after IVF. Hum Reprod 2003; 18: 2328-36.
38. Saunders K, Spensley J, Munro J, Halasz G. Growth and physical outcome of children conceived by in vitro fertilization. Pediatrics1996; 97: 688-92.
39. Makhoul IR, Tamir A, Bader D, et al. In vitro fertilization and use of ovulation enhancers may both influence childhood height in very low birthweight infants. Arch Dis Child Fetal Neonatal Ed 2009; 94: 355-9.
40. Miles HL, Hofman PL, Peek J, et al. In vitro fertilization improves childhood growth and metabolism. J Clin Endocrinol Metab 2007; 92: 3441-5.