

In Vitro Fertilization Sonrası İkiz Gebeliklerin Antepartum, İntrapartum ve Perinatal Sonuçları

Mehmet GÜNEY, Baha ORAL, Tamer MÜNGAN, Demir ÖZBAŞAR

Department of Obstetrics and Gynecology, Faculty of Medicine, Süleyman Demirel University, Isparta, Turkey

Received 09 February 2006; received in revised form 12 April 2006; accepted 12 May 2006

Abstract

Antepartum, Intrapartum and Perinatal Outcome of Twin Pregnancies After *In Vitro* Fertilization

Objective: The aim of this study was to evaluate antepartum, intrapartum and perinatal complications in spontaneous versus *in vitro* fertilization twins.

Materials and Methods: We conducted a retrospective cohort study of twin pregnancies delivered at the Süleyman Demirel University, Faculty of Medicine, Department of Obstetrics and Gynecology and Isparta Women's and Children's Hospital between 1999 and 2005. Controls were identified from spontaneous multiple pregnancies delivered in the same time period. A total of 52 cases and 104 controls were studied. They were compared with respect to various maternal and neonatal complications.

Results: Mean maternal age, the proportion of nulliparous women, the incidence of premature rupture of membranes, cesarean section, and premature delivery were significantly higher in the study group. The cesarean delivery rate was significantly higher in cases of twins who were conceived by *in vitro* fertilization (84% vs 67%, $p<0.05$). The preterm delivery rate was also significantly higher (55% vs 47%, $p<0.05$) and no significant difference was present between the groups with respect to the gestational age (34 ± 4 weeks vs 35 ± 3 weeks). The number of perinatal deaths, stillbirths, fetal distress, cord prolapse, and neonatal intensive care unit admissions was similar in both groups.

Discussion: When compared with control twins, *in vitro* fertilization twins are more likely to be delivered by cesarean delivery and to have a higher incidence of preterm birth. This study provides further evidence for a different outcome of *in vitro* fertilization twin pregnancies in comparison with spontaneously conceived twin pregnancies.

Keywords: *in vitro* fertilization, multiple pregnancy, perinatal outcomes

Özet

Amaç: Spontan ve IVF ikiz gebeliklerinin antepartum, intrapartum ve perinatal sonuçlarını karşılaştırmak.

Materyal ve Metot: 1999-2005 yılları arasında Süleyman Demirel Üniversitesi Tıp Fakültesi Kadın Hastalıkları ve Doğum Kliniği ile Isparta Kadın Hastalıkları ve Doğum Hastanesi'ndeki ikiz gebeliklerde retrospektif kohort bir çalışma gerçekleştirdik. Kontrol grubu çalışma grubu ile aynı zamanda gebe kalan spontan ikiz gebeliklerden oluşturuldu. Toplam 52 *in vitro* fertilizasyon ikiz gebeliği ile 104 spontan ikiz gebelik olgusu çalışmaya alındı. Her iki grup çeşitli maternal ve neonatal komplikasyonlar yönünden karşılaştırıldı.

Sonuç: Ortalama anne yaşı, nullipar olgu oranı, erken membran rüptürü sıklığı, sezaryen ve erken doğum sıklığı çalışma grubunda anlamlı olarak daha sıklı. *In vitro* fertilizasyon grubunda sezaryen doğum oranı anlamlı olarak daha yüksekti (%84 -67, $p<0.05$). Preterm doğum oranı çalışma grubunda kontrol grubu ile karşılaştırıldığında daha yüksek iken (%55-47) gruplar arasında gebelik yaşı yönünden fark yoktu (34 ± 4 ile 35 ± 3 hafta). Her iki grupta perinatal ölüm, ölü doğum, fetal distress, kordon sarkması ve yenidoğan yoğun bakım tedavisi sayıları benzer idi.

Tartışma: Spontan ikiz gebeliklerle karşılaştırıldığında *in vitro* fertilizasyon ikiz gebeliklerinde sezaryen ve preterm doğum sıklığı daha fazla idi. Bu çalışma spontan ikiz gebeliklerle karşılaştırıldığında *in vitro* fertilizasyon ikiz gebeliklerinin sonuçlarına ilişkin ilave kanıtlar ortaya koymaktadır.

Anahtar sözcükler: *in vitro* fertilizasyon, çoğul gebelik, perinatal sonuçlar

Corresponding Author: Dr. Mehmet Güney
Süleyman Demirel Üniversitesi Tıp Fakültesi,
Kadın Hastalıkları ve Doğum AD, Isparta, Türkiye
Phone : +90 246 223 87 84
E-mail : mguney@med.sdu.edu.tr

Introduction

With increasing rates of infertility and a delay in childbearing until later in life, the demand for assisted reproductive technologies has grown. The increased rate of multiple pregnancies in recent years has been attributed to assisted reproductive technology, with twin gestations accounting 20% to 25% of all pregnancies conceived after this procedure (1). This is comparatively higher than the spontaneous conception rates of 1.05% to 1.35% for twins and 0.01% to 0.017% for triplets (2).

In vitro fertilization pregnancies have been associated with relatively high rates of fetal loss and ectopic pregnancies as well as high rates of prematurity, low birth weight and perinatal complications (3,4). Multiple gestations are associated with prematurity, low birth weight, pregnancy-induced hypertension, gestational diabetes, postpartum hemorrhage, and increased perinatal morbidity and mortality (5).

The perinatal outcome of pregnancies obtained by *in vitro* fertilization is worse than that for spontaneously conceived pregnancies (6). Infertility itself could increase the risk of small-for-gestational age and preterm birth, although some authors did not confirm these relationships (7-9). Studies comparing the pregnancy outcome in spontaneous versus IVF twin gestations report inconsistent results. Some have shown an increase in perinatal mortality, higher rates of preterm delivery, and lower birth weight in IVF multiple pregnancies (3,10). Others have described no difference or even lower risk of adverse outcome in induced twinning and this relatively better outcome has been mainly ascribed to the low incidence of monozygous twins in assisted reproductive technology pregnancies (11,12).

The purpose of the present study was to compare perinatal outcome in the twins conceived by IVF with spontaneously conceived multiples.

Materials and Methods

We conducted a retrospective study of the twin pregnancies delivered at the Süleyman Demirel University, Faculty of Medicine, Department of Obstetrics and Gynecology and Isparta Women's and Children's Hospital between 1999 and 2005. Clinical data were collected through the patients' obstetrical files. Miscarriages (less than 24 weeks) and birth weights less than 500 g were excluded from the study. Women who underwent ovulation induction only and multifetal pregnancy reduction and women who had an underlying maternal disease that may have increased the risk of specific pregnancy complications (ie, preexisting hypertension, pregestational diabetes mellitus, or renal disease) were also excluded. In addition, twins conceived through intracytoplasmic sperm injection were excluded from the study. Information on maternal age, parity, mode of conception, mode of delivery, obstetric complications (preterm labor, preterm delivery, hypertensive disorders of pregnancy, and intrauterine growth restriction [IUGR]), and maternal hospital stay was extracted from maternity records for each mother. The elective cesarean delivery rates were compared between the groups. Pre-

maturity, growth discordance, Apgar scores, need for admission to intensive care nursery (NICU) and major neonatal morbidity and perinatal mortality rates were reviewed with the use of nursery records in order to assess the neonatal outcome.

Gestational age was calculated from the date of embryo transfer plus two weeks for the IVF pregnancies, and according to the last menstrual period and the first-trimester ultrasound estimation for the naturally conceived pregnancies. Pregnancy induced hypertension was defined as persistent blood pressure of $\geq 140/90$ mmHg after 20 weeks of gestation in previously normotensive women, while preeclampsia was diagnosed whenever pregnancy-induced hypertension was accompanied with proteinuria of ≥ 300 mg per 24 h or abnormal hematological or biochemical markers or associated symptomatology. Oligohydramnios and polyhydramnios were diagnosed whenever the amniotic fluid index was < 5 cm and > 18 cm, respectively. Uterine bleeding was defined as any bleeding episode during pregnancy. Diagnosis of gestational diabetes mellitus was based on a 3-h 100 g oral glucose tolerance test. Preterm birth was considered whenever delivery occurred before 37 weeks of gestation. The low birth weight rate (LBW, < 2500 g), very low birth weight rate (VLBW, < 1500 g), and the NICU admission were evaluated for each group. Perinatal outcomes were assessed according to the low Apgar scores at 1 and 5 min of neonatal life. Low apgar scores were considered as ≤ 4 at 1 min and ≤ 7 at 5 min (13). Perinatal deaths consisted of stillbirths of all babies weighing ≥ 500 g and liveborn neonates who died within 7 days of delivery. Complications during delivery (intrapartum) including fetal distress, cord prolapse, chorioamnionitis, and instrumental delivery were estimated as well.

The statistical analysis was conducted using Statistical Package for Social Sciences version 9.0 (SPSS Inc., Chicago, IL, USA). Maternal characteristics and neonatal complications were compared by χ^2 test. The one-way analysis of variance (Anova) was used to compare the means of the groups. Statistical significance was defined as $p < 0.05$.

Results

The study included 156 twin deliveries. The study group consisted of 52 pregnancies conceived by IVF and the control group consisted of 104 naturally conceived pregnancies. The mean maternal age of the study group was significantly higher than in the control group (30.7 ± 4.7 vs 26.7 ± 4.1 years) (Table 1). Nulliparous women were significantly more in the IVF group whereas multiparous women were significantly more in the control group ($p < 0.05$). *In vitro* fertilization twins were more likely to have preterm labor (71% vs 58%, $p < 0.05$), OR (95%CI) 1.95 (0.96-3.96) and a premature rupture of membranes (15% vs 6%, $p < 0.05$), OR (95%CI) 2.51 (0.89-7.12) compared with control subjects. Twenty-nine IVF patients (55%) and 49 control subjects (47%) were delivered before the completion of 37 weeks of gestation ($p < 0.05$). There was a significant difference between the subjects who delivered before the completion of 37 weeks of gestation. Eight IVF subjects (15%) and 9 control subjects (9%) were delivered before 32 weeks of gestation. The difference between the

Table 1. Maternal and demographic characteristics of the study and control twin groups

Characteristic	IVF twins (n=52)	Spontaneous twins (n=104)	OR (95% CI)	p
Maternal age(years)*	30.9±4.7	26.7±4.1		<0.05
Parity				
Multiparity	10 (19%)	64 (61%)	0.15 (0.07-0.32)	<0.05
Nulliparity	42 (81%)	40 (39%)	6.72 (0.006-14.69)	<0.05
Preterm labor	37 (71%)	58 (56%)	1.95 (0.96-3.96)	<0.05
Gestational diabetes	2 (3%)	2 (1%)	2 (0.34-11.69)	
Oligohydramnios	1 (2%)	1 (1%)	2.02 (0.2-19.77)	
Polihydramnios	0 (0)	0 (0)		
Placenta previa	2 (3%)	2 (1%)	2 (0.34-11.69)	
Preeclampsia	3 (5%)	3 (2%)	1.98 (0.44-8.91)	
Uterine bleeding	4 (7%)	4 (4%)	2.08 (0.54-7.95)	
Intrauterine fetal death	1 (2%)	2 (1%)	1 (0.12-7.85)	
Ablatio placenta	0 (0)	1 (1%)		
Pregnancy induced HT	4 (7%)	5 (4%)	1.65 (0.45-5.96)	
PROM	8 (15%)	7 (6%)	2.51 (0.89-7.12)	<0.05
Birthweight*	2.090±615 g	2.210±684 g		
Cerclage	2 (3%)	2 (1%)	2.04 (0.34-11.92)	
Maternal hospital stay*	6±2	5±3		
Monozigotic twin	2 (3%)	21 (20.5%)	0.15 (0.04-0.63)	<0.05
Received steroid	32 (61%)	14 (13%)	10 (4.68-22.6)	<0.05

*Data are given as mean±SD.
HT: hypertension; PROM: premature rupture of membranes; IVF: *In vitro* fertilization

groups was also significant ($p<0.05$). No differences were seen in the incidences of hypertensive disorders of pregnancy, oligohydramnios, polihydramnios, placenta previa, preeclampsia, birthweight and intrauterine fetal death. More patients received steroids to enhance fetal lung maturity in the IVF group (61% vs 13%, $p<0.05$), OR (95%CI) 10 (4.68-22.6).

Table 2 summarizes labor characteristics observed in the IVF and the control groups. The rate of cesarean section was significantly higher in the IVF group (84% vs 67%, $p<0.05$), OR (95%CI) 2.67 (1.15-6.18). The rates of fetal distress, cervical cerclage and cord prolapse were similar in two groups. The elective cesarean delivery rate was significantly higher in the IVF group compared with the control group (80% vs 59%, $p<0.05$), OR (95%CI) 2.84 (1.30-6.20).

Table 3 summarizes perinatal and neonatal characteristics observed in the IVF and the study groups. The ratio of subjects who gave birth to LBW neonates in the IVF group was significantly lower than that in the spontaneous twin group. There were no statistically significant differences in the frequency of VLBW, male and female gender, NICU admission, perinatal deaths, congenital anomalies, and stillbirth.

Discussion

The outcome of multiple gestations resulting from assisted reproductive techniques has been a subject of controversy. Patients want to know the safety and quality of the outcome that they will have when they undergo medical intervention to achieve pregnancy. Some believe that the resulting pregnancy may be more complicated than that originating from spontaneous conception

Table 2. Labor characteristics in IVF and the spontaneous twin groups

Variable	IVF twins (n=52)	Spontaneous twins (n=104)	OR (95% CI)	p
Gestational age (years)*	34±4	35±3		
Premature delivery (weeks)				
<32	8 (15%)	9 (9%)	1.91 (0.71-5.16)	<0.05
<37	29 (55%)	49 (47%)	1.41 (0.72-2.75)	<0.05
Induction of labor	4 (7%)	18 (17%)	0.39 (0.13-1.19)	<0.05
Fetal distress	3 (5%)	5 (5%)	0.121 (0.30-4.80)	
Cord prolapse	0	2 (2%)		
Cesarean delivery	44 (84%)	70 (67%)	2.67 (1.15-6.18)	<0.05
Elective cesarean delivery	42 (80%)	62 (59%)	2.84 (1.30-6.20)	<0.05

*Data are given as mean±SD.

Table 3. Perinatal and neonatal characteristics of the IVF and the spontaneous twin groups

Variable	IVF pregnancies (n=52)	Spontaneous pregnancies (n=104)	OR (95%CI)	p
Apgar score				
1 min ≤4	8 (15%)	11 (10%)	1.53 (0.59-3.99)	<0.05
5 min ≤7	13 (25%)	17 (16%)	1.70 (0.76-3.81)	
Congenital anomalies	2 (3%)	4 (3%)	1.00 (0.20-4.86)	
Birthweigh				
LBW <2.500 g	34 (65%)	53 (50.9%)	1.81 (0.94-2.42)	<0.05
VLBW <1.500 g	8 (15%)	11 (10%)	1.53 (0.59-3.99)	
Male gender	24 (46%)	51 (49%)	0.89 (0.45-1.72)	
Female gender	28 (54%)	49 (51%)	1.31 (0.67-2.54)	
NICU admission	23 (44%)	42 (40%)	1.17 (0.6-2.28)	
Perinatal deaths	3 (3%)	4 (3%)	1.53 (0.36-5.38)	
Stillbirths	1 (2%)	4 (3%)	0.49 (0.07-3.38)	
LBW: low birth weight VLBW: very low birth weight NICU : neonatal intensive care unit				

because of advanced maternal age and factors related to the cause of infertility (14).

The patients in the IVF group were older and more often nulliparae. Older women are more prone for antepartum complications such as hypertensive disorders, gestational diabetes, preterm labor, and increased cesarean delivery rate compared with younger women (14). IVF patients are, on average, older and more often primiparous than the average population (15,16). When specific pregnancy complications were studied, a significant difference was found only in premature rupture of membranes, as it was shown by a previous study (11). Several studies where cases were matched for age and parity also fail to demonstrate any significant difference in pregnancy complications (11,17). Peterson et al. prospectively compared 90 IVF pregnancies with 90 non-IVF pregnancies (17). Rates of preeclampsia, preterm labor, intrauterine growth restriction, and abruptio placentae were similar. Their study concluded that the birth weights of twins were not significantly different between IVF and control groups. Olivennes et al. found no difference in the global rate of prematurity in their comparison of twin pregnancies obtained after IVF with those obtained spontaneously or after ovarian stimulation (11). However, they could not demonstrate that very premature deliveries (prior to 31 weeks of gestation) were more frequent in the IVF group. Fitzsimmons et al. found that mean gestational age at delivery, birth weight, rate of preterm labor, preterm premature rupture of membranes, pregnancy-induced hypertension, neonatal morbidity, and incidence of gestational diabetes were not significantly different between the IVF pregnancies and controls when controlled for age, parity, and the absence of medical problems (12). In our study pregnancy-induced hypertension, neonatal morbidity, incidence of gestational diabetes, placenta previa, cerclage, uterine bleeding, and ablatio placenta were not significantly different among the groups.

In the present study, the frequency of IVF conceptions was significantly higher in older women, as shown by the previous studies (18). Our data showed an increased tendency toward a lower gestational age at delivery in IVF twins. *In vitro* fertilization twins

have an increase in preterm births from 32 to 36 weeks of gestation compared with spontaneously conceived twins who were matched for maternal age (OR, 1.48; 95% CI, 1.05-2.10). The OR for preterm birth at <37 weeks of gestation in studies that also matched for parity was similar and approached statistical significance at a 5% level of significance (OR 1.47; 95% CI, 1.01-2.44) (19). In our study OR (95% CI) was found as 1.41 (0.72-2.75) which was similar to previous studies. The origin of the increase in preterm birth has yet to be determined. Possible causes include a factor inherent to the IVF technology, a history of infertility itself, or physician or patient anxiety. Moise et al. found that 60% of IVF twins were born prematurely, compared to only 40% of the control twins (3). We found that 71% of IVF twins were born prematurely, compared to only 56% of the control twins. Minakami et al. found no differences in gestational age at birth and birthweight in twin pregnancies after various forms of medically assisted conception as compared to spontaneously conceived twin pregnancies, despite the fact that the mono chorionic placenta rate was significantly higher in the spontaneous group (57% versus 2.2%) (20). Some factors that may contribute to the complications, such as prematurity and low birth weight in IVF twin pregnancies have been identified and related to the hyperstimulation of the endometrium, diseased tubes, age and parity of the patient, and above all, the high incidence of multiple pregnancy (7).

Olivennes et al. compared perinatal outcome of 154 twins from IVF with 164 spontaneously conceived twins and found that no associated increase in adverse perinatal outcomes was present (11). In our study, there were four perinatal deaths in the control group, whereas three twins died during the perinatal period in the IVF group. There was no apparent difference in the distribution of causes of perinatal death, although it can be presumed that the higher frequency of preterm birth is one of the contributing factors. The lower (approximately 2%) incidence of monozygous twins in IVF, compared with the one third incidence in spontaneously conceived twins, suggests that IVF twins should have better outcomes than spontaneously conceived twins, yet they do not (19). Among the causes of perinatal death, hypertensive disorders were not encountered more frequently in the

IVF group. A number of reports have indicated that preeclampsia occurs more frequently in IVF pregnancies (21,22). Our findings are not necessarily in concordance with these observations, but indicate that preeclampsia was not a contributor to the increased perinatal mortality. In our study, we found that the perinatal mortality of twins were not significantly different between the IVF and control groups. We found that the mean birth weight of the IVF twins was significantly lower than that of the controls. In general, >50% of twins weigh <2500 g at birth which is more than six times the rate of LBW in singletons. Moise et al. (3) reported that almost 60% of the control twins were LBW, as were 70% of the IVF twins. In our study, 50% of the control twins and 65% of the IVF twins were LBW. When the LBW infants were further divided into LBW and VLBW categories, the difference between the two groups was marked.

An increased rate of cesarean delivery rate in induced twin pregnancies has been described in many studies and was observed in our study (16,11,15). It was suggested that most of the cesarean deliveries in IVF twins are performed because of anxiety encompassing the management of these 'premium' pregnancies making the obstetricians threshold for intervention lower (15). Most studies found an increased rate of cesarean delivery, although the Swedish cohort did not, which perhaps reflects national differences in physician or patient attitudes towards the mode of delivery (19). The worse outcome of induced twinning may be partially attributed to the higher incidence of elderly primiparae in the study group for pregnancy complications, cesarean section, and less favorable pregnancy outcome. The increased incidence of prematurity due to premature rupture of membranes in our IVF group may be a contributing factor for worse outcomes. Olivennes et al. (11) observed a similar rate of premature rupture of membranes in their IVF group. This complication is associated with prematurity, perinatal mortality, and neonatal morbidity and may contribute to the higher rate of prematurity observed in the study group (23,24). In our study when only preterm rupture of membranes and premature twins were studied, the outcome was poorer in induced twins, having lower birthweight, shorter duration of pregnancy, and lower 5 minute Apgar score.

There are growing concerns about the increased risks of congenital malformations in children who are born after IVF, including cardiac and neural tube defects (19). The incidence of congenital malformations is significantly higher in IVF pregnancies compared with the general population (3% vs 1.7%) (11). However, Mc Donald et al. in their meta-analyses showed no significant differences in perinatal mortality rates, the proportion of SGA infants, or the rate of congenital malformations (19).

The shortcomings of our data should be noted. The small size of population is one of the most serious limitations of this study as well as the retrospective nature of the study. No exhaustive information was collected on congenital malformation and chromosomal abnormalities. Furthermore, the data concerning clear information about population characteristics like educational status and chronic diseases were restricted.

In conclusion, this study provides further evidence for a different outcome of IVF twin pregnancies in comparison with naturally conceived gestations. *In vitro* fertilization twin pregnancies are more likely to experience premature rupture of membranes and undergo a cesarean section. *In vitro* fertilization twins are at increased risk for premature delivery, lower birthweight, and higher perinatal morbidity in comparison with spontaneously conceived twins. It remains unclear whether the IVF twin pregnancies have an unfavorable effect in outcomes of twin gestation. Longer data series are needed to validate or rebut our results.

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