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Dilemma of Increased Obstetric Risk in Pregnancies Following IVF-ET

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***Purpose*:** To determine the rates of pregnancy complications following in vitro fertilization in comparison with those in a matched control group.
***Methods*:** A total of 13,543 deliveries at the Department of Obstetrics and Gynecology, University of Szeged, between January 1, 1995 and February 28, 2002 were subjected to retrospective analysis. The 230 (1.7%) pregnancies following IVF-ET were evaluated and matched with spontaneous pregnancies concerning age, parity, gravidity, and previous obstetric outcome. Demographic and selected maternal characteristics, pregnancy and labor complications, and neonatal outcome were compared in the two groups.
***Results*:** The pregnancy complication rate was partly significantly higher among the singleton IVF-ET pregnancies. The obstetric risk was elevated, though not significantly concerning twin pregnancies.
***Conclusions*:** IVF-ET presents an additional obstetric risk. The neonatal outcome displays a significant difference only concerning an increased premature birth rate of singleton pregnancies. Triplet IVF-ET pregnancies involve a much higher risk of both pregnancy complications and neonatal outcome.

KEY WORDS: IVF-ET; matched control; pregnancy complications.

INTRODUCTION

In vitro fertilization (IVF-ET) has played a crucial role in the treatment of infertility since 1978 (1), and serves as the basis of various assisted reproductive techniques. During recent decades, IVF-ET has become a widespread realistic alternative for infertile couples. The major concerns about the obstetric risk of pregnancy after IVF-ET are related to the higher rate of multiplicity, previous infertility, primiparas over 35 and the technique itself (2). Studies on the obstetric outcome of such pregnancies, and especially twin gestations (3,4), have revealed differences from those conceived naturally. Higher rates of preterm deliveries, low birthweight of infants, a shorter duration of gestation, cesarean section, placenta previa, and pregnancy-induced hypertension after IVF-ET have been reported (5–7). Some reports concluded that there is an increased risk of congenital malformation (8,9), though others did not (10). When controlled for maternal age, parity, ethnic origin, and location of delivery, singleton IVF pregnancies have been reported not to involve an increased risk of prematurity, low birthweight, maternal or fetal complications (11). However, matched controls have yielded adverse results as concerns IVF-ET (3,11–14).

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MATERIALS AND METHODS

A total of 13,543 deliveries at the Department of Obstetrics and Gynecology, University of Szeged, between January 1, 1995 and February 28, 2002 were subjected to retrospective analysis. The 230 (1.7%) of these deliveries were after IVF. A total of 185 singleton and 36 twin pregnancies were evaluated and matched to spontaneous pregnancies as controls as regards age, parity, gravidity, and previous obstetric outcome. The samples were comparable. The 13 triplet pregnancies were observed and analyzed in crude distribution. Demographic and other selected maternal characteristics, pregnancy and labor complications, and neonatal outcome were compared between the two groups. The following antepartum complications were examined: gestational diabetes mellitus, preeclamptic toxemia, myoma, placenta previa, malpresentation, placental abruption, premature rupture of the membranes, intrauterine infection, oligohydramnios, and polyhydramnios. The following intrapartum characteristics were assessed: cesarean section, fetal distress, fetopelvic disproportion, retained placenta, postpartum hemorrhage, prolonged labor, and prolonged second stage. Macrosomia was taken as a birthweight of $\geq$4000 g. Small for gestational age (SGA) was defined as a birthweight below the 10th percentile for that gestational age, according to the Hungarian data (15). Intrauterine infection was recorded when the mother had fever and leukocytosis, and the neonate had tachycardia. Fetal distress was defined as the presence of repetitive late decelerations, severe variable decelerations and persistent fetal tachycardia. The body mass index (BMI) was calculated as the body weight (kg) per height (m^2).

Statistical analysis was performed with the SPSS 8.0 Windows program (16). Differences in the characteristics of the outcomes of singleton pregnancies between the two groups were assessed by the Fisher exact test for categorical variables and the Student *t* test for continuous variables. Odds ratios (ORs) and 95% confidence intervals (CIs) were also calculated for categorical variables. Comparisons between the twin groups were performed with the Mann–Whitney *U* test and the Wilcoxon test for categorical and ordinal variables. The significance level was set at 5%, two-tailed.

RESULTS

The maternal characteristics in the two groups are presented in Tables I and II for the singleton and twin pregnancies, respectively. The singleton IVF-ET mothers were significantly higher educated ($P < 0.05$), while the mothers of twins also had a higher educational level, but the difference did not reach the level of significance. The BMI before delivery did not differ between the two groups, whereas the weight gain during pregnancy was significantly higher among the singleton IVF-ET and the spontaneously conceived twin mothers. The rates of primiparity and primigravidity did not differ statistically significantly between the two groups, reflecting the success of the matching procedure. Congenital anomalies of the uterus were more common among singleton IVF-ET pregnancies, but without a significant difference.

Table I. Selected Maternal Characteristics in Singleton Pregnancies

	IVF-ET group ($n = 185$)		Spontaneous group ($n = 185$)			
	n	%	*n*	%	*P* value	OR (95% CI)
Education						
Elementary or less	25	13.5	8	4.3		
Secondary	88	47.6	97	52.4		
Higher	72	38.9	80	43.2	<0.05	
BMI (kg/m^2) (mean $\pm$ SD)	28.02 $\pm$ 5.26		28.15 $\pm$ 4.70		ns	
Weight at delivery (kg) (mean $\pm$ SD)	76.09 $\pm$ 14.65		75.84 $\pm$ 12.38		<0.05	
Primiparity	69	37.3	74	40.0	ns	0.89 (0.59–1.36)
Congenital anomalies of uterus[a]	7	3.8	1	0.5		

Note. OR: Odds ratio; CI: Confidence interval; ns: Statistically not significant.
[a] Statistical analysis was not performed due to the low number of entries.

Table II. Selected Maternal Characteristics in Twin Pregnancies

	IVF-ET group ($n = 36$)		Spontaneous group ($n = 36$)		P value
	n	%	n	%	
Education					
Elementary or less	4	10.8	6	18.9	
Secondary	16	43.2	21	56.8	ns
Higher	16	45.9	9	24.3	
BMI (kg/m^2) (mean ± SD)	28.15 ± 3.73		28.76 ± 4.65		ns
Weight at delivery (kg) (mean ± SD)	72.8 ± 16.50		78.94 ± 15.64		<0.05
Primiparity	23	63.9	15	41.7	ns
Primigravidity	16	44.4	11	30.6	ns
Congenital anomalies of uterus	0	0.0	0	0.0	ns

Note. ns: Statistically not significant.

Table III overviews the differences in birth outcome between the two groups. The birthweight of the neonates was significantly lower, whereas the incidence of prematurity was significantly higher among the IVF-ET cases. Statistical differences were not observed as concerns the gestational age and the rate of SGA. Macrosomia was significantly more common among the spontaneous pregnancies.

Table IV relates to the neonatal outcome in the twin groups. Surprisingly, the birthweight of the IVF-ET twin neonates was significantly higher. The gestational age of the IVF-ET twins was longer, while the rates of premature birth and SGA were similar.

The pattern of pregnancy complications in the surveyed groups are detailed in Table V. Threatened preterm delivery was significantly more prevalent among the IVF-ET pregnancies. Almost all pregnancy complications occurred with higher frequency among the IVF-ET pregnancies, with the exception of meconium-stained amniotic fluid, intrauterine infection, and oligohydramnios. The rates of myoma, placental abruption, and polyhydramnios were extremely low in both singleton groups.

Table IV. Neonatal Outcome in Twin Pregnancies

	IVF-ET group ($n = 72$)		Spontaneous group ($n = 72$)		P value
	n	%	n	%	
Birth weight (g) (mean ± SD)	2305.7 ± 565.7		2166.0 ± 662.6		<0.05
Gestational age (weeks) (mean ± SD)	35.25 ± 2.72		34.70 ± 3.26		ns
Premature birth	50	67.6	46	63.9	ns
SGA	22	30.6	22	30.6	ns
Macrosomia	0	0.0	0	0.0	

Note. ns: Statistically not significant.

Table VI lists the data on the characteristics of the twin pregnancies. There were no statistically significant differences between the case and control twin groups in the rates of most obstetric complications. Gestational diabetes mellitus, preeclampsia, threatened preterm delivery, inertia uteri, meconium-stained amniotic fluid, malpresentation, and premature rupture of the membranes exhibited similar rates in both groups. The rates of myoma, placenta previa, placental abruption, oligohydramnios, and polyhydramnios were very low in both groups.

Surprisingly, significant increases in cephalopelvic disproportion, prolonged labor, and a prolonged second stage were noted in the control singleton pregnancies. The incidence of cesarean section was noteworthy in IVF-ET pregnancies, but the difference did not reach the level of statistical significance (Table VII).

Table III. Neonatal Outcome in Singleton Pregnancies

	IVF-ET group ($n = 185$)		Spontaneous group ($n = 185$)		P value	OR (95% CI)
	n	%	n	%		
Birthweight (g) (mean ± SD)	3116.2 ± 592.8		3323.5 ± 566.94		<0.05	
Gestational age (weeks) (mean ± SD)	38.06 ± 2.30		38.74 ± 1.77		ns	
Premature birth	29	15.7	14	7.6	<0.05	2.27 (1.16–4.45)
SGA	15	8.1	8	4.3	ns	1.95 (0.81–4.72)
Macrosomia	8	4.3	21	11.4	<0.05	0.35 (0.15–0.82)

Note. OR: Odds ratio; CI: Confidence interval; ns: Statistically not significant.

Table V. Pregnancy Characteristics in Singleton Pregnancies

	IVF-ET group ($n = 185$)		Spontaneous group ($n = 185$)			
	n	%	*n*	%	*P* value	OR (95% CI)
Gestational diabetes mellitus	12	6.5	10	5.4	ns	1.21 (0.51–2.88)
Preeclampsia	25	13.5	21	11.4	ns	1.22 (0.66–2.27)
Myoma[a]	2	1.08	3	1.6		
Placenta previa[a]	1	0.5	0	0.0		
Threatened preterm delivery	52	28.1	21	11.4	< 0.001	3.05 (1.75–5.32)
Inertia uteri	144	77.8	128	69.2	ns	1.56 (0.98–2.49)
Meconium-stained amniotic fluid	22	11.9	31	16.8	ns	0.67 (0.37–1.21)
Malpresentation	15	8.1	10	5.4	ns	1.54 (0.68–3.53)
Abruptio placentae[a]	2	1.08	0	0.0		
Premature rupture of the membranes	67	36.2	65	35.1	ns	1.05 (0.69–1.60)
Intrauterine infection	11	5.9	17	9.2	ns	0.62 (0.28–1.37)
Oligohydramnios	7	3.8	11	5.9	ns	0.62 (0.24–1.64)
Polyhydramnios[a]	3	1.6	0	0.0		

Note. OR: Odds ratio; CI: Confidence interval; ns: Statistically not significant.
[a] Statistical analysis was not meaningful.

The rates of intrapartum complications in the twin study groups were comparable. The difference in the incidence of cesarean section was considerable, but did not attain statistical signifcance (Table VIII).

Table IX demonstrates the high rates of selected obstetric characteristics among the triplet pregnancies. The rates of cesarean section (100%) and threatened preterm delivery (92.3%) indicate the elevated obstetric risk, and the rates of prematurity (53.8%) and SGA (43.6%) the increased neonatal risk in this group.

DISCUSSION

The high frequency of cesarean section observed in our study accords with previous literature reports (3,11–14), though the difference in our matched control study did not reach the level of significance.

Table VI. Pregnancy Characteristics in Twin Pregnancies

	IVF-ET group ($n = 36$)		Spontaneous group ($n = 36$)		
	n	%	*n*	%	*P* value
Gestational diabetes mellitus	5	13.9	3	8.3	ns
Preeclampsia	6	16.7	5	13.9	ns
Myoma[a]	0	0.0	0	0.0	
Placenta previa[a]	0	0.0	1	2.8	
Threatened preterm delivery	27	75.0	28	77.8	ns
Inertia uteri	30	83.3	34	94.4	ns
Meconium-stained amniotic fluid	1	2.8	4	11.1	ns
Malpresentation	10	27.8	13	36.1	ns
Abruptio placentae[a]	2	5.6	3	8.3	
Premature rupture of the membranes	17	47.2	22	61.1	ns
Intrauterine infection	3	8.3	4	11.1	ns
Oligohydramnios[a]	1	2.8	1	2.8	
Polyhydramnios[a]	1	2.8	0	0.0	

Note. ns: Statistically not significant.
[a] Statistical analysis was not meaningful.

Table VII. Intrapartum Complications in Singleton Pregnancies

	IVF-ET group ($n = 185$)		Spontaneous group ($n = 185$)			
	n	%	*n*	%	*P* value	OR (95% CI)
Fetal distress	48	25.9	45	24.3	ns	1.09 (0.68–1.74)
Cephalopelvic disproportion	9	4.9	23	12.4	<0.05	0.36 (0.16–0.80)
Cesarean section	78	42.2	69	37.3	ns	1.23 (0.81–1.86)
Retained placenta	16	8.6	13	7.0	ns	1.25 (0.59–2.68)
Postpartum hemorrhage[a]	2	1.08	0	0.0		
Prolonged labor	19	10.3	34	18.4	<0.05	0.51 (0.28–0.93)
Prolonged second stage	7	3.8	20	10.8	<0.05	0.32 (0.13–0.79)

Note. OR: Odds ratio; CI: Confidence interval; ns: Statistically not significant.
[a] Statistical analysis was not meaningful.

Table VIII. Intrapartum Complications in Twin Pregnancies

	IVF-ET group ($n = 36$)		Spontaneous group ($n = 36$)		
	n	%	*n*	%	*P* value
Fetal distress	5	13.9	6	16.7	ns
Cephalopelvic disproportion[a]	2	5.6	0	0.0	
Cesarean section	27	75.0	21	58.3	ns
Retained placenta	6	16.7	4	11.1	ns
Postpartum hemorrhage[a]	0	0.0	1	2.8	
Prolonged labor	4	11.1	4	11.1	ns
Prolonged second stage[a]	1	2.8	2	5.6	

Note. ns: Statistically not significant.
[a] Statistical analysis was not meaningful.

The significantly higher frequency of threatened preterm delivery in the case group reflects the significantly increased rate of prematurity. Despite this phenomenon, the mean gestational age did not differ significantly. The overall pregnancy and labor complication rates were comparable and controversial.

The rate of pregnancy-induced hypertension (not tabulated) was <1% in both the case and the control group, which is in contrast with the high incidence observed among IVF-ET pregnancies in previous reports. Further, our study did not confirm the higher incidence of placenta previa found in other studies (12,13); this can probably be explained by the different technique of ET.

A number of reports involving matched controls have drawn attention to the high incidence of preterm deliveries and SGA after IVF-ET (3,12,13), but this was not the case in other papers (11,14). In our study, the incidences of SGA and premature delivery proved to be higher after IVF-ET, but without attaining the level of statistical difference.

Table IX. Selected Perinatal Characteristics in Triplet Pregnancies ($n = 13$)

	n	%
Cesarean section[a]	13	100
Threatened preterm delivery[a]	12	92.3
EPH-gestosis[a]	2	15.4
PROM[a]	3	23.1
Preterm birth[b]	21	53.8
SGA[b]	17	43.6
5-min. Apgar score <7[b]	8	20.5
Male newborns[b]	22	56.4
Cord blood pH <7.20[b,c]	7/36	19.4
Congenital anomalies[b]	2	5.1

[a] Regarding the number of mothers.
[b] Regarding the number of newborns.
[c] Examination was not performed in every case.

In some previous matched control studies, the mean gestational age and mean birthweight at delivery were significantly lower in IVF-ET infants (3,12,13) or neonates of twin pregnancies (14), but another study did not find the same result (11). In contrast with earlier corresponding studies, we observed no major difference in respect of gestational age. The twin IVF-ET pregnancies resulted in a higher birthweight, whereas the opposite held true for the singleton pregnancies.

IVF-ET involves only a partly increased obstetric risk. The neonatal outcome exhibits a minimal difference as compared with that for naturally conceived pregnancies, with a significantly higher rate of premature birth in singleton pregnancies. The rate of triplet pregnancies following IVF-ET should be minimized in view of the much higher risk as concerns both the obstetric and the perinatal outcome.

REFERENCES

1. Steptoe PC, Edwards RG: Birth after the reimplantation of a human embryo. Lancet 1978;2:366
2. Bergh T, Ericson A, Hillensjo T, Nygren KG, Wennerholm UB: Deliveries and children born after in-vitro fertilisation in Sweden 1982–95: A retrospective cohort study. Lancet 1999;354:1579–1585
3. Koudstaal J, Braat DDM, Bruinse HW, Naaktgeboren N, Vermeiden JPW, Visser GHA: Obstetric outcome of singleton pregnancies after IVF: A matched control study in four Dutch University hospitals. Hum Reprod 2000;15:1819–1825
4. Lambalk CB, van Hooff M: Natural versus induced twinning and pregnancy outcome: A Dutch nationwide survey of primiparous dizygotic twin deliveries. Fertil Steril 2001;4:731–736
5. Lancaster PAL: Australian In Vitro Fertilization Collaborative Group. High incidence of preterm births and early losses in pregnancy after IVF. BMJ 1985;291:1160–1163
6. Doyle P, Beral V, Maconochie N: Preterm delivery, low birth weight and small-for-gestational-age in liveborn singleton babies resulting from in-vitro fertilization. Hum Reprod 1992;7:425–428
7. Seoud MA, Toner JP, Kruithoff C, Muasher SJ: Outcome of twin, triplet and quadruplet in vitro fertilization pregnancies: The Norfolk experience. Fertil Steril, 1992;57:825–834
8. Hansen M, Kurinczuk JJ, Bower C, Webb S: The risk of major birth defects after intracytoplasmic sperm injection and in vitro fertilization. N Eng J Med 2002;346:725–730
9. Ericson A, Källen B: Congenital malformations in infants born after IVF: A population-based study. Hum Reprod 2001;16:504–509
10. Bonduelle M, Liebaers I, Deketerlaere V, Derde M-P, Camus M, Devroey P, Steirteghem AV: Neonatal data on a cohort of 2889 infants born after ICSI (1991–1999) and of 2995

infants born after IVF (1983–1999). Hum Reprod 2002;3:671–694
11. Reubinoff BE, Samueloff A, Friedler S, Schenker JG, Lewin A: Is the obstetric outcome of in vitro fertilized singleton gestations different from natural ones? A controlled study. Fertil Steril, 1997;67:1077–1083
12. Tan SL, Doyle P, Campbell S, Beral V, Risk B, Brinsden P: Obstetric outcome of in-vitro fertilization pregnancies compared with normally conceived pregnancies. Am J Obstet Gynecol 1992;167:778–784
13. Verlaenen H, Cammu H, Derde MP, Amy JJ: Singleton pregnancy after in-vitro fertilization: Expectations and outcome. Obstet Gynecol 1995;86:906–910
14. Koudstaal J, Bruinse HW, Helmerhorst FM, Vermeiden JPW, Willemsen WNP, Visser GHA: Obstetric outcome of twin pregnancies after in-vitro fertilization: A matched control study in four Dutch University hospitals. Hum Reprod 2000;15: 935–940
15. Hungarian Statistical Office: Demographic Year Book. Budapest, Hungarian Statistical Office, 2001
16. SPSS for Windows, Chicago: SPSS, 1999 (software)