

## Original article

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# Perinatal Outcomes of Preterm Twins <34 Weeks after IVF Pregnancies versus Natural Conception: Same Oral Feeding Tolerance?

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**Purpose:** To compare the oral feeding tolerance that reflects a general maturity of organization of behavior and response among preterm twins less than 34 weeks of gestation conceived after in vitro fertilization with/without embryo transfer (IVF-ET) with that of natural conception.

**Methods:** Medical records of 135 preterm twins less than 34 weeks of gestation (74 twins conceived after IVF-ET and 61 spontaneously conceived twins) admitted to the Neonatal Intensive Care Unit (NICU) of Dong-A Medical Center during the period from January 2003 to December 2010 were used for a retrospective study. The primary study outcomes were perinatal mortality and overall short term morbidity. The secondary study outcome was oral feeding tolerance.

**Results:** There was no difference among the two groups in the gestational age and birth weight. Perinatal mortality rate and morbidity rate was not different between the two groups. In terms of feeding practice, there was no significant difference in terms of the starting date of first enteral feeding ( $4.1 \pm 4.5$  days vs.  $3.5 \pm 3.6$  days, IVF-ET twin group vs. spontaneous twin group), the time it took to reach full enteral feeding ( $26.7 \pm 20.5$  days vs.  $27.6 \pm 24.3$  days), the time it took to reach full oral feeding ( $34.4 \pm 21.7$  days vs.  $34.3 \pm 24.1$  days) and PMA upon full oral feeding ( $36.0 \pm 2.2$  weeks vs.  $36.0 \pm 1.8$  weeks), the duration of total parenteral nutrition ( $23.1 \pm 21.0$  days vs.  $24.9 \pm 24.3$  days), displaying similar oral feeding tolerance.

**Conclusion:** There was no difference in oral feeding tolerance between two groups.

**Key Words:** In vitro fertilization and embryo transfer, Oral feeding tolerance, Preterm, Twin pregnancy, Neonatal outcome

## Introduction

In vitro fertilization (IVF) and embryo transfer (ET) were attempted on human beings for the first time in 1965 by Edwards. Since then, the number of infants born through IVF-ET is on the rise due to an increase in the number of older-age mothers and recent development of various assisted reproductive technology (ART)<sup>1</sup>. The rate of multiple fetuses as a result of IVF is reportedly

15–30%, known to be 20 to 30 times higher than the rate of spontaneous multiple fetuses<sup>2</sup>. Compared to single pregnancy, multiple pregnancy is more prone to maternal and perinatal complications including miscarriage, premature birth, congenital anomaly, low birth weight, hypertension during pregnancy, gestational diabetes and placenta previa, and thus is categorized as high risk pregnancy<sup>3</sup>. However, it is not clearly known whether twins conceived after IVF-ET (hereinafter referred to as “IVF-ET

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twins<sup>7</sup>) have greater risks than spontaneously conceived twins (hereinafter referred to as “spontaneous twins”<sup>4</sup>). Some studies reported that IVF-ET twins had similar perinatal prognosis to that of spontaneous twins<sup>4-8</sup>, but on the contrary, there have been reports that the former had higher frequency of premature birth, perinatal mortality, risks involved with C-section, low birth weight and congenital anomaly<sup>9,10</sup>. Oral feeding intolerance is a major cause that delays discharge from NICU. However, among the perinatal prognosis factors evaluated by existing studies, there was no comparison involving enteral feeding, or in particular oral feeding. The type of feeding (enteral-oral, gastric, transpyloric or parenteral delivery) is determined after monitoring an infant’s adaptability based on the level of enteral maturity, gestational age, birth weight, sucking ability, muscle tension level, and sucking-swallowing-breathing coordination<sup>11</sup>. Although sucking starts inside the mother’s uterus at 15 to 18 weeks of gestational age, when infants reaches 34 weeks post-menstrual age (PMA), the aforementioned reactions generally are known to stabilize and to become well-patterned<sup>12</sup>. Therefore, the disorganized suck pattern during oral feeding reflects a general immaturity of organization of behavior and response<sup>13</sup>.

Therefore, authors performed overall comparative analysis of perinatal prognosis factors of preterm twins (<34 weeks of gestation after IVF-ET pregnancies compared with natural conception, and attempted to determine the differences of oral feeding practice.

## Materials and Methods

Medical records of preterm twins (<34 weeks of gestation admitted to the Neonatal Intensive Care Unit (NICU) of Dong-A Medical Center during the period from January 2003 to December 2010 were used for a retrospective study. Of the 148 preterm twins (<34 weeks of gestation, cases of expired or transferred before reaching full enteral feeding and lack of medical record were excluded. Finally, 74 twins after IVF-ET and 61 twins after naturally conception were enrolled.

Included in the survey were mothers’ age, birth history (primiparous vs. multiparous), clinical chorioamnionitis, pathologic confirmed chorioamnionitis, premature rupture of

membrane (PROM), preterm labour, antenatal hemorrhage, preeclampsia, placenta previa, gestational diabetes mellitus (GDM), antenatal steroid and body mass index at delivery (BMI). The type of procedure used for conception through IVF-ET was not considered. Clinical chorioamnionitis was defined as a fever (>37.8°C) plus two or more of the following: maternal tachycardia (>100 beats/min), fetal tachycardia (>160 beats/min), uterine tenderness, malodorous or cloudy amniotic fluid, maternal white blood cell count >15,000 cells/mm<sup>3</sup>. Pathologic confirmed chorioamnionitis was diagnosed when chorioamnionitis was confirmed by placenta pathology.

As for infants, gestational age (GA), birth weight, gender, Apgar scores at one minute/five minutes, small for gestational age (SGA), discordant twin, delivery method (spontaneous delivery, elective cesarean section, emergency cesarean section), congenital anomaly, cord blood pH were examined. In terms of neonatal prognosis factors, respiratory distress syndrome (RDS), use of surfactant, duration of ventilator use, oxygen treatment duration, bronchopulmonary dysplasia (BPD), transient tachypnea of newborn (TTN), patent ductus arteriosus (PDA), intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), retinopathy of prematurity (ROP), sepsis, hyperbilirubinemia, necrotizing enterocolitis (NEC), duration of NICU admission, and mortality rate were investigated. RDS was defined as respiratory difficulty in preterm infants with characteristic chest X-ray appearance (uniform reticular pattern and air-bronchogram). BPD was defined as an oxygen dependency for the first 28 days of life by Jobe’s criteria<sup>14</sup>. TTN was defined respiratory distress shortly after delivery with prominent perihilar streaking that usually resolved within 3-5 days, retrospectively. PDA was defined as cases of treatment with indomethacin. IVH was limited to high grade with ventricular dilatation (≥Grade III)<sup>15</sup>. ROP was limiting to a high stage requiring laser therapy. Sepsis was diagnosed when there were clinical signs of systemic infection with a positive blood culture. NEC was defined as a high grade (≥Grade II) by modified Bell’s staging criteria<sup>16</sup>. For feeding practice, premature infants less than 34 weeks of gestation started with intermittent oro-gastric tubal feeding and then switched to oral feeding when they reached PMA 34 weeks of gestation. Feeding started as early as possible once an infant’s

conditions were stable, and breast milk was given as a priority. In accordance with the hospital's feeding policy, the feeding started with 15–20 mL/kg/day on the first day with a priority given to enteral nutrition, and if the feeding practice was going well, the amount was increased to 20 mL/kg/day. The feeding interval was three hours. Feeding was stopped when following cases took place: milk vomiting more than two times a day, bilious or bloody vomiting, abdominal distension with/without visible bowel loop, gastric residues of at least one-half of the previous gavage volume, and clinical signs and symptoms suggestive of necrotizing enterocolitis, tachypnea during the oral feeding practice ( $>60$  rates/min), reduced oxygen saturation requiring oxygen supply and bradycardia ( $<100$  beats/min). When the enteral feeding amount reached 150 mL/kg/day, it was defined as full enteral feeding, and when the oral feeding amount reached 150 mL/kg/day, it was defined full oral feeding. As prognosis factors involved with feeding practice, the starting date of enteral feeding after birth, the time it took to reach full enteral feeding (150 mL/kg/day by enteral feeding), the time it took to reach full oral feeding (150 mL/kg/day by oral feeding), PMA upon full oral feeding, and the duration of total parenteral nutrition (TPN) (central TPN, peripheral TPN, intravenous fluid) were investigated.

The study was approved by the Institutional Review Board of the Dong-A Medical Center.

All the statistical values are shown as average  $\pm$  standard deviation, and SPSS 18.0 for windows (SPSS Inc., Chicago, IL, USA) was used for the analysis. Two-tailed tests were used for all the statistical tests, and only when the value of *P* was less than 0.05 was the data believed to have statistical significance. To compare the frequency and proportion of categorical variables, a Chi-square test (Fisher's exact test) was used. To analyze differences in the average between two independent groups, a Student's *t*-test was used.

## Results

### 1. Maternal characteristics

Clinical characteristics of mothers of twins conceived after IVF-ET and mothers of spontaneously conceived twins were

analyzed (Table 1). The average age of mothers of IVF-ET twins was  $31.7 \pm 3.0$  years, which was not significantly different from that of the mothers of spontaneous twins at  $31.5 \pm 4.9$  years. The ratio of primiparous mother was 43.2% for the IVF-ET twins group, which was not significantly different from that of the spontaneous twins group at 34.4%. BMI at delivery was similar in both the groups ( $25.9 \pm 3.4$  kg/m<sup>2</sup> versus  $25.9 \pm 7.3$  kg/m<sup>2</sup>). When obstetric complications are compared, there was no significant difference between the two groups in terms of PROM, premature labour, chorioamnionitis, antenatal hemorrhage, placenta previa, preeclampsia, GDM and use of antenatal steroid.

### 2. Neonatal characteristics

The comparison of the infants found that the average gestational age and birth weight of the IVF-ET twins group were  $31.2 \pm 2.1$  weeks of gestation and  $1,666.7 \pm 432.3$  g, respectively, which were not much different from those of the spontaneous group at  $31.1 \pm 2.4$  weeks of gestation and  $1,687.5 \pm 431.5$  g, respectively. Comparison of birth weight found no difference in terms of frequency of low birth weight (LBW) ( $<2,500$  g) and of very low birth weight (VLBW) ( $<1,500$  g). As for the delivery method, there was no difference between the two groups, but both the groups had much more cases of births through C-section rather than natural deliveries. Apart from this, there was no difference in

**Table 1. Maternal Characteristics in the IVF-ET and Spontaneous Twins**

Variables	IVF-ET, N=74 (%)	Spontaneous, N=61 (%)	<i>P</i>
Age, years	31.7 $\pm$ 3.0	31.5 $\pm$ 4.9	0.76
Primiparous	32 (43.2)	21 (34.4)	0.38
Clinical chorio	10 (13.5)	5 (8.2)	0.41
Pathologic chorio	4 (5.4)	2 (3.3)	0.69
PROM	10 (13.5)	14 (22.9)	0.18
Preterm labour	49 (66.2)	49 (80.3)	0.08
Antenatal hemorrhage	4 (5.4)	0	0.69
Placenta previa	6 (8.1)	4 (6.6)	0.77
Preeclampsia	6 (8.1)	1 (1.6)	0.13
GDM	2 (2.7)	4 (6.6)	0.41
Antenatal steroid	38 (51.4)	24 (39.3)	0.17
BMI at delivery	25.9 $\pm$ 3.4	25.9 $\pm$ 7.3	0.96

Abbreviations: N, number; Chorio, chorioamnionitis; PROM, premature rupture of membrane; GDM, gestational diabetes mellitus; BMI, body mass index.

terms of the frequency of SGA, discordant twins, gender, Apgar scores at one-minute/five-minute, congenital anomaly (two cases of cleft lip and palate and tracheoesophageal fistula for IVF-ET twins group) and cord blood pH (Table 2).

### 3. Perinatal outcomes

In terms of the morbidity rate of neonatal illnesses and premature infant illnesses, the two groups did not show significant difference in RDS, use of surfactant, duration of ventilator use, duration of oxygen treatment, BPD, TTN, PDA, IVH, PVL, ROP, sepsis, hyperbilirubinemia, NEC, duration of NICU admission and mortality rate (Table 3).

In terms of the feeding practice, the starting date of the first enteral feeding for the IVF-ET twins group was  $4.1 \pm 4.5$  days after birth, which was not much different from the spontaneous twins group's  $3.5 \pm 3.6$  days. Since then, enteral feeding was introduced and it took  $26.7 \pm 20.5$  days for the IVF-ET twin group to reach enteral feeding of 150 mL/kg/day, whereas for the spontaneous twin group, it took  $27.6 \pm 24.3$  days, indicating that both the groups took similar time to reach full enteral feeding.

**Table 2.** Neonatal Characteristics in the IVF-ET and Spontaneous Twins

Variables	IVF-ET, N=74 (%)	Spontaneous, N=61 (%)	<i>P</i>
GA, weeks	31.2±2.1	31.1±2.4	0.67
Bwt, g	1,666.7±432.3	1687.5±431.5	0.78
LBW (<2,500 g), N	73 (98.6)	60 (98.4)	1.00
VLBW (<1,500 g), N	26 (35.1)	21 (34.4)	1.00
SGA	5 (6.8)	3 (4.9)	0.73
Discordant twin	21 (28.4)	12 (19.7)	0.32
Male	36 (48.6)	23 (37.7)	0.23
Delivery method			0.81
NSVD	4 (5.4)	2 (3.3)	
Elective C/S	4 (5.4)	4 (6.6)	
Emergency C/S	66 (89.2)	55 (90.2)	
AS 1	5.6±1.7	5.4±2.2	0.40
AS 5	7.9±1.0	7.6±1.8	0.21
Anomaly	2 (2.7)	0	0.50
Cord pH	7.1±1.2	7.3±0.1	0.21

Abbreviations: N, number; GA, gestational age; Bwt, birth weight; LBW, low birth weight; VLBW, very low birth weight; SGA, small for gestational age; NSVD, normal spontaneous vaginal delivery; C/S, cesarean section; AS 1, Apgar score at one minute; AS 5, Apgar score at five minutes.

The time it took for oral feeding to reach 150 mL/kg/day was compared to find that it took  $34.4 \pm 21.7$  days for the IVF-ET twins group and  $34.3 \pm 24.1$  days for the spontaneous twins group, which means that the time to reach full oral feeding did not show significant difference statistically. PMA upon full oral feeding was compared to find that it was  $36.0 \pm 2.2$  weeks of gestation for the IVF-ET twins group and  $36.0 \pm 1.8$  weeks of gestation for the spontaneous twins group, showing no significant difference statistically. The duration of TPN was not different between two groups ( $23.1 \pm 21.0$  days for the IVF-ET twin group vs.  $24.9 \pm 24.3$  days for the spontaneous twins group) (Table 4).

**Table 3.** Comparison of Perinatal Outcomes between the IVF-ET and Spontaneous Twins

Variables	IVF-ET, N=74 (%)	Spontaneous, N=61 (%)	<i>P</i>
RDS	24 (32.4)	26 (42.6)	0.28
Surfactant	24 (32.4)	21 (34.4)	0.86
Ventilator (days)	6.0 ±12.8	6.6±13.8	0.80
Oxygen (days)	3.0±5.5	5.1±8.8	0.10
BPD	2 (2.7)	5 (8.2)	0.24
TTN	8 (10.8)	5 (8.2)	0.77
PDA	14 (18.9)	14 (23.0)	0.67
IVH	0	1 (1.6)	0.45
PVL	0	2 (3.3)	0.20
ROP	1 (1.4)	0	0.45
Sepsis	8 (10.8)	13 (2.1)	0.07
Hyperbilirubinemia	72 (97.3)	57 (93.4)	0.41
NEC	2 (2.7)	4 (6.6)	0.41
Hospital stay (days)	43.9±23.6	42.9±27.9	0.83
Death	0	0	NS

Abbreviations: N, number; RDS, respiratory distress syndrome; BPD, bronchopulmonary dysplasia; TTN, transient tachypnea of newborn; PDA, patent ductus arteriosus; IVH, intraventricular hemorrhage; PVL, periventricular leukomalacia; ROP, retinopathy of prematurity; NEC, necrotizing enterocolitis.

**Table 4.** Outcome Variables of Enteral Feeding between the IVF-ET and Spontaneous Twins

Variables	IVF-ET, N=74	Spontaneous, N=61	<i>P</i>
Start enteral feed (days)	4.1±4.5	3.5±3.6	0.37
Full enteral feed (days)	26.7±20.5	27.6±24.3	0.82
Full oral feed (days)	34.4±21.7	34.3±24.1	0.97
PMA at full oral feed (weeks)	36.0±2.2	36.0±1.8	0.84
Total parenteral nutrition (days)	23.1±21.0	24.8±24.3	0.65

Abbreviations: N, number; PMA, post-menstrual age.

## Discussion

About 10–15% of couples in the reproductive age group suffer from infertility, and recent development of various assisted reproductive technologies is offering more opportunities for infertile couples<sup>17)</sup>. While patients who undergo in vitro fertilization are mainly interested in higher success rate of pregnancy, delivery of healthy and normal infants is actually more important. Recently, perinatal prognosis is being improved thanks to prenatal care, effective methods for early diagnosis of multiple fetus pregnancy, adequate use of fetus monitoring device, and development and improvement of infant treatment. The rate of multiple pregnancy among spontaneous conception is less than 1%, and while the same rate varies for IVF-ET from one researcher to another, the frequency of multiple pregnancy is known to be about 20 times higher in the case of IVF-ET compared to spontaneous conception<sup>18–20)</sup>. Of multiple pregnancy, twins pregnancy accounts for over 80%. Prior research found that twins pregnancy has higher frequency of maternal complications such as preeclampsia and GDM, as well as preterm birth, and cesarean section, and higher possibility of perinatal complications among the newborn<sup>21)</sup>. Studies that compared obstetric complications and perinatal prognosis among IVF-ET twins and spontaneous twins offer different views from one researcher to another. Most of this is attributable to differences in research methods, and while there is a research outcome that there was no notable difference between the two groups, there have been research outcomes that showed significant difference<sup>2,5,17,22,23)</sup>.

Messer A, et al.<sup>7)</sup> and Vasario E, et al.<sup>4)</sup>, in their recent studies, reported that there was no difference between the IVF-ET twins group and the spontaneous twins group in terms of mothers' clinical characteristics and the newborn's perinatal prognosis. On the contrary, McDonald SD, et al.<sup>10)</sup> reported that the frequency of premature infants between 32 weeks of gestation and 36 weeks of gestation and C-section was higher among the IVF-ET twins group, while Kallen B, et al.<sup>9)</sup> suggested that delivery of premature infants less than 32 weeks of gestation was more frequent among the IVF-ET twins group and more cases of jaundice were also found in this group. In this study, there was no difference in terms

of the mothers' clinical characteristics. Other than this, there was no difference between the two groups in terms of perinatal and neonatal prognosis. And even when the fact that most of such prognosis factors are related to premature babies was taken into consideration for further comparison, no significant difference could be found between the two groups.

Premature infants often experience difficulty when they go from gavage feeding to oral feeding. This is a main cause of prolonged admission at a hospital, causing distress in mothers and higher financial burden from hospital admission<sup>11)</sup>. Immature sucking, delayed swallow and/or uncoordinated suck, swallow and respiration are potential causes for oral feeding issues. Suck is primarily controlled by the suck central pattern generator, which includes bilateral, internuncial circuits within the brainstem reticular formation<sup>11)</sup>. Mechanical maturation of oral feeding skills need to occur at the peripheral and central levels, i.e. muscles and central nervous system<sup>12)</sup>. In terms of oral feeding practice, full oral feeding is reached with increasing PMA in reflection of general maturation. Therefore, this study considers comparison of oral feeding practice between the IVF-ET twins group and the spontaneous twins group as an important factor for a perinatal outcome, and compared the starting point of enteral feeding, the time it took to reach full enteral feeding and the time it took to reach full oral feeding and the PMA at the time of full oral feeding.

In general, oral feeding is tried at 34 weeks of gestation when sucking–swallowing–respiration coordination can be achieved, and even for a premature infant over 34 weeks of gestation, if the infant has difficulty in oral feeding, gavage feeding is introduced at the same time. In comparison of prognosis factors related to feeding practice for the two groups, the starting time of enteral nutrition was  $4.1 \pm 4.5$  days in the IVF-ET twins group and  $3.5 \pm 3.6$  days in the spontaneous twins group, indicating little difference. Meanwhile, the IVF-ET twins group reached full enteral feeding (150 mL/kg/day by enteral feeding) in  $26.7 \pm 20.5$  days, whereas it took  $27.6 \pm 24.3$  days for the spontaneous twins group to reach full enteral feeding ( $P=0.82$ ). Oral feeding started at PMA 34 weeks, and it took  $34.4 \pm 21.7$  days for the IVF-ET twins group to reach full oral feeding (150 mL/kg/day by oral feeding), which is somewhat delayed compared to the spontaneous twins group's  $34.3 \pm 24.1$  days, but no significant difference statistically



( $P=0.97$ ). In addition, PMA of the two groups when they reached full oral feeding was compared to find that there was no difference, with  $36.0\pm 2.2$  weeks of gestation for the IVF-ET twins group and  $36.0\pm 1.8$  weeks of gestation for the spontaneous twins group ( $P=0.84$ ).

In conclusion, there was no difference in the morbidity rate of neonatal and perinatal illnesses. In particular, with respect to oral feeding practice, the two groups had no difference in terms of full enteral feeding, as well as the time required to reach full oral feeding and PMA at the time of full oral feeding, confirming that oral feeding tolerance, too, was similar. As for obstetric prognosis, there was no significant difference in terms of occurrence of obstetric complications.

This study is meaningful because it confirmed that there is no difference among the IVF-ET twins group and spontaneous twins group in oral feeding practice through a comparison of the two groups' perinatal outcomes. However, it has a limitation in that it had small number of study subjects and it failed to include specific feeding skills to confirm the maturational process of oral feeding, as the study is a retrospective study using medical records. Hence, a process to support this study's outcomes through a prospective study is considered necessary in the future.

## 한글요약

**목적:** 재태 연령 34주 미만의 체외수정기술 쌍생아와 자연 임신 쌍생아를 대상으로 전반적인 성숙도를 반영하는 경구 수유 진행에 차이에 있는지 알고자 하였다.

**방법:** 2003년 1월부터 2010년 12월까지 동아대학교 병원 신생아 집중치료실에 입원하였던 재태 연령 34주 미만 135명(자연 임신 쌍생아 74명, 체외수정기술쌍생아 61명)을 대상으로 의무기록지를 이용하여 후향적으로 연구하였다. 연구의 일차 목적은 두 군간 주산기 사망률과 단기 유병률을 비교하는 것이고, 이차 목적은 경구 수유 진행의 차이를 보는 것이다.

**결과:** 두 군의 평균 재태 연령, 평균 출생체중은 차이가 없었다. 두 군간 주산기 사망률 및 단기 유병률에 의미 있는 차이는 없었다. 수유 진행 상태를 비교하였을 때 첫 장관 수유 시작일( $4.1\pm 4.5$ 일 vs.  $3.5\pm 3.6$ 일, 체외수정기술 쌍생아군 vs. 자연 임신 쌍생아군), 완전 장관 수유 도달일( $26.7\pm 20.5$ 일 vs.  $27.6\pm 24.3$ 일), 완전 경구 수유 도달

일( $34.4\pm 21.7$ 일 vs.  $34.3\pm 24.1$ 일), 완전 경구 수유 도달 시 주수( $36.0\pm 2.2$ 주 vs.  $36.0\pm 1.8$ 주), 인공 영양 사용일( $23.1\pm 21.0$ 일 vs.  $24.9\pm 24.3$ 일)에 두 군간 의미 있는 차이가 없었다.

**결론:** 체외수정기술 쌍생아와 자연 임신 쌍생아간에 주산기 사망률, 단기 유병률 및 경구 수유 진행에 차이가 없었다.

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