Short-term and long-term outcomes of trichorionic triplet pregnancies with expectant management

Ji Yeon Lee1 • Seung Mi Lee2 • Mina Jeong2 • Sohee Oh3 • Subeen Hong2 • Seung-Ah Choe4 • Jong Kwan Jun2,5

Abstract

Introduction: Reproductive endocrinologists recommend selective multifetal pregnancy reduction (MFPR) to save at least one or two babies, because triplet pregnancy is known to increase the risk of miscarriage and preterm delivery. However, recently improved obstetric and neonatal care may affect pregnancy outcomes differently in triplet pregnancies, which could alter practice. We compared the maternal, perinatal, and long-term outcomes of triplet pregnancies managed expectantly with those of pregnancies reduced to twins.

Material and methods: In this retrospective cohort study, we reviewed the clinical records of 552 trichorionic triplet pregnancies for obstetric, perinatal, and neurodevelopmental outcomes, which consisted of the expectant management (EM) group (n = 225) and MFPR group (n = 327), in Seoul National University Hospital and CHA Bundang Medical Center from January 2006 to December 2018. Neuromotor development was evaluated using the Korean-Ages and Stages Questionnaire, Bayley-III tests, and/or Gross Motor Function Measure. The two groups were compared for the following outcomes: (1) nonviable pregnancy loss before 23 weeks, (2) preterm birth before 34 weeks of gestation, (3) fetal and neonatal survival and (4) long-term neurodevelopmental outcomes.

Results: There were no differences in maternal age, body mass index, nulliparity or previous preterm birth between the two groups. The risk of nonviable pregnancy loss was lower in the EM group than that in the MFPR group (2 [0.9%] vs 21 [6.4%, p = 0.001]. The risk of preterm delivery before 34 weeks of gestation was lower in the MFPR group (adjusted odds ratios [aOR] = 0.47, 95% confidence interval [CI] 0.30–0.73, p = 0.001). The survival rate of neonates until discharge (644 [95.4%] vs 572 [87.5], p < 0.001) and the rate of pregnancies with at least one survivor (220 [97.8%] vs 301 [92.0], p = 0.002) were higher in the EM group than those in the MFPR group.
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INTRODUCTION

Advanced maternal age and the wide application of fertility treatment have led to an increase in multiple gestations. Twins, triplets and higher-order multiple gestations now account for more than 3% of all live births. It is well known that multiple gestation is associated with an increased risk of maternal complications, as well as high perinatal morbidity and mortality.

Because triplet or higher-order multiple gestations are more likely to develop these risks, several preventive strategies to limit the number of fetuses have been suggested. Elective single-embryo transfer and multifetal pregnancy reduction (MFPR) are the recommended methods for this purpose. In contrast to elective single-embryo transfer, which is a relatively acceptable and useful method, MFPR is a more complicated method in clinical practice, involving a number of medical, economic, psychological and ethical issues. Moreover, triplet pregnancies are more common than quadruplet or higher-order pregnancies, making MFPR in triplet pregnancy a more challenging subject.

As MFPR is not easily acceptable for infertile couples, more clear evidence is required to recommend MFPR in triplet pregnancy. Most data advocating MFPR in triplet pregnancy were derived from the comparison of maternal and perinatal outcomes between twin and triplet pregnancies, although direct comparisons of outcomes between continuing triplets and reduced twins from triplets are more desirable. To show the usefulness of MFPR for triplet pregnancy, improved maternal and neonatal morbidity and mortality in reduced twins from triplets should be demonstrated, but few studies have been conducted from these points of view. Multifetal reduction of a quadruplet or higher-order pregnancy to twins has been advocated, with data showing that MFPR prolongs gestational age and increases birthweight. Nonetheless, there are conflicting data about whether pregnancies reduced from triplets to twins fare better than expectantly managed triplet pregnancies. Moreover, most studies were conducted several years or decades ago. Maternal and fetal morbidity and mortality should be carefully assessed based on contemporary data. To clarify this issue, we conducted this study to compare the maternal, perinatal and long-term outcomes of triplet pregnancies managed expectantly with those of pregnancies reduced to twins.

In the MFPR group, the risk of developmental delay (aOR = 2.89, 95% CI 1.38–6.02, p = 0.005) was higher.

Conclusions: In trichorionic triplet pregnancies, the possibility of EM to improve survival and reduce the risk of developmental delay has been shown.

KEYWORDS
expectant management, fetal survival, multifetal pregnancy reduction, neurodevelopmental outcome, triplet pregnancy
was chosen. After the procedure, a first-generation cephalosporin, ampicillin or amoxicillin was administered prophylactically.

The two groups were compared for the rates of nonviable pregnancy loss before 23 weeks, the rates of preterm birth, and the number of surviving fetuses. Maternal obstetric complications, such as preeclampsia and gestational diabetes, were also evaluated. Preeclampsia was defined by high blood pressure (≥140/90 mm Hg) and one or more of the following complications after 20 weeks of pregnancy: proteinuria (≥300 mg/24 h), or urine protein: creatinine ratio ≥3.0, or dipstick 1+ persistently, thrombocytopenia (platelet count <100 000/μL), renal insufficiency (creatinine level >1.1 mg/dL or doubling of baseline), impaired liver function, new onset of headaches or visual disturbances. Gestational diabetes was defined as abnormal in the 100-g oral glucose tolerance test according to the Carpenter–Coustan criterion.

To evaluate the short-term birth outcomes, we investigated neonatal survival and composite morbidities, defined as the occurrence of at least one of the following: neonatal sepsis, intracranial hemorrhage, retinopathy of prematurity, patent ductus arteriosus, pulmonary hypertension, respiratory distress syndrome, bronchopulmonary dysplasia and necrotizing enterocolitis. We evaluated small-for-gestational age using the standard described in a previous report.

We investigated the long-term neurodevelopmental outcomes after 1 year of corrected age. Developmental delay was diagnosed when babies did not reach their developmental milestones at the expected times. It was evaluated using the Korean-Ages and Stages, Bayley-III tests and/or Gross Motor Function Measure in our study. When the score acquired in the tests was below the normal development reference, this was determined to be developmental delay. If not tested, we checked the medical records that described the child’s developmental status. We considered development to be normal in children who reported no difficulty in fulfilling their normal academic obligations. Most babies who had been treated in the neonatal intensive care unit underwent these developmental tests during their regular visit to the pediatric outpatient clinic after discharge. Babies born healthy at late preterm or full term with no suspicion of developmental disorders were not tested. The diagnosis of cerebral palsy (CP) was made by satisfying the following four conditions that correspond to the definition of CP at least 1 year after birth: (i) immature brain, (ii) nonprogressive brain lesions or injury, (iii) impairment of movement and posture and (iv) a pattern of clinical syndrome that can change as the child grows. For the diagnosis of CP, a detailed medical history was obtained, and close physical examinations including muscle tone, hyperopia, spontaneous exercise and posture reflection were performed by a pediatric neurologist, pediatric rehabilitation specialist or child developmental specialist. In addition, complementary information was obtained through brain ultrasonography, brain computed tomography, brain magnetic resonance imaging, evoked potentials (auditory evoked potentials, visual evoked potentials, somatosensory evoked potentials) and/or electroencephalography. We confirmed that the diagnosis for CP did not change in the second year of life.

2.1 | Statistical analyses

Statistical analysis was performed using SPSS version 23.0 (SPSS Institute) and R (R Foundation for Statistical Computing). We analyzed discrete data using Chi-square test or Fisher’s exact test, and comparisons of continuous variables were performed with the Student t test or the Mann-Whitney U test. A generalized estimating equation was used to calculate a risk estimates for each of neonatal outcomes, accounting for the within-sibling correlation of the same mother. We also performed a multivariable analysis including maternal age, body mass index (BMI), method of conception and interval time between study and data collection as covariates, when analyzing a baby’s survival or morbidities. A p value < 0.05 was considered statistically significant.

2.2 | Ethical approval

The institutional review boards (IRB) of Seoul National University Hospital Clinical Research Institute (IRB no.: H-1311-045-533, date of approval: 11 April 2014) and CHA Bundang Medical Center approved this study (IRB no.: C 2016-10-007, date of approval: 13 October 2016).

3 | RESULTS

After excluding monochorionic or dichorionic triplets, we identified 552 trichorionic triplet pregnancies, which included 225 EM cases and 327 MFPR cases.

Table 1 shows the clinical characteristics of the study population. There were no differences in the mean maternal age and BMI and the frequency of nulliparity and history of preterm birth between the two groups. The proportion of in vitro fertilization pregnancy was higher in the MFPR group than in the EM group. In the EM group, there were significantly more cases with antenatal administration of steroids (betamethasone or dexamethasone) or antibiotics than in the MFPR group. However, the frequency of antenatal magnesium sulfate administration did not differ between the two groups.

Table 2 compares the obstetric outcomes between the two groups. In the EM group, the risk of preterm delivery (<36, <34, <32 and <28 weeks) was higher than that in the MFPR group. However, in the EM group, the risk of nonviable pregnancy loss was lower (2 [0.9%] vs 21 [6.4%, p = 0.001]) than that in the MFPR group. Moreover, the rate of cases with at least one live neonate was higher (220 [97.8%] vs 301 [92.0%, p = 0.002]). In terms of obstetric complications, the risk of preeclampsia (30 [13.3%] vs 17 [5.2%, p = 0.001]) was higher in the EM group than in the MFPR group, whereas there was no evidence of a difference in the risk of gestational diabetes and postpartum hemorrhage between the two groups. Even after adjustment for maternal age, BMI and method of conception, the risk of nonviable fetal loss (adjusted odds ratios [aOR] = 14.87, 95% confidence interval [CI] 1.89–117.04, p = 0.010) and the rate of no
neonatal survivor (aOR = 5.87, 95% CI 1.66–20.73, p = 0.006) were significantly higher in the MFPR group, whereas the risk of preterm delivery and preeclampsia was lower in the MFPR group than in the EM group.

The study population included 1329 fetuses: 675 in the EM group and 654 in the MFPR group (Table 3). The survival rate of neonates until 2 h after birth (649 [96.1%] vs 579 [88.5%], p < 0.001) and the survival rate of neonates until discharge (644 [95.4%] vs 572 [87.5], p < 0.001) were also significantly higher in the EM group than in the MFPR group. Higher rates of ongoing pregnancies before 32 weeks of gestation were observed in the EM group than in the MFPR group (Figure 1).

Preterm birth (87.9%) due to preterm labor or preterm premature rupture of the membranes was a common reason for the end of intrauterine fetal survival before 30 weeks of pregnancy in the EM group and fetal death in utero (75.9%) in the ER group (Table S1).

After adjustment for maternal age, BMI, method of conception, steroids administration, magnesium sulfate administration and antibiotic use, the risk of neonatal sepsis (aOR = 3.62, 95% CI 1.82–7.21, p < 0.001), retinopathy of prematurity (aOR = 2.28, 95% CI 1.09–4.74, p = 0.028) and respiratory distress syndrome (aOR = 1.74, 95% CI 1.07–2.82, p = 0.024) was higher in the MFPR group, but the risk of patent ductus arteriosus (aOR = 0.48, 95% CI 0.28–0.82, p = 0.007), and bronchopulmonary dysplasia (aOR = 0.20, 95% CI 0.07–0.62, p = 0.005) was lower in the MFPR group (Table 4).

We evaluated the risk of developmental delay and CP in 1161 babies. In some cases, two diagnostic methods were used to diagnose developmental delay, but there was no discrepancy between the results of the two tests (Table S2). The risks of developmental delay (aOR = 2.89, 95% CI 1.38–6.02, p = 0.005) was higher in the MFPR group after adjustment for maternal age, BMI, method of conception, steroids administration, magnesium sulfate administration and antibiotic use. Although the risk of CP showed a higher trend in MFPR, there was no statistically significant difference between the two groups after adjustment for the above factors.

Table 1: Clinical characteristics of the study population

|                        | Expectant management (n = 225) | Multifetal pregnancy reduction (n = 327) | p value |
|------------------------|-------------------------------|------------------------------------------|---------|
| Maternal age (year)a   | 33.2 ± 3.4                    | 33.6 ± 3.9                               | 0.064   |
| Height (cm)a           | 162.1 ± 5.3                   | 161.4 ± 5.4                              | 0.876   |
| BMIa                   | 22.0 ± 3.4                    | 21.8 ± 3.4                               | 0.379   |
| Nulliparityb           | 193 (85.8)                    | 280 (85.6)                               | 0.532   |
| Prior preterm birthb   | 2 (0.9)                       | 8 (2.4)                                  | 0.153   |
| Method of conception   |                               |                                          |         |
| Spontaneousb           | 9 (4.0)                       | 12 (3.7)                                 | <0.001  |
| Ovarian stimulationb   | 94 (41.8)                     | 49 (15.0)                                |         |
| In vitro fertilizationb| 122 (54.2)                    | 266 (81.3)                               |         |
| Maternal medical conditions |                             |                                          |         |
| Pregestational diabetesb | 2 (0.9)                      | 0 (0.0)                                  | 0.166   |
| Hyperthyroidismb       | 1 (0.4)                       | 0 (0.0)                                  | 0.408   |
| Hypothyroidismb        | 2 (0.9)                       | 2 (0.6)                                  | 0.538   |
| Asthmab                | 0 (0.0)                       | 1 (0.3)                                  | 0.592   |
| Hepatitis Bb           | 5 (2.2)                       | 2 (0.6)                                  | 0.102   |
| Medication administered after 23 weeks of GA | (N = 223) | (N = 306) |         |
| Steroidsb              | 88 (39.5)                     | 59 (19.3)                                | <0.001  |
| Magnesium sulfateb     | 23 (10.3)                     | 39 (12.7)                                | 0.236   |
| Antibioticsb           | 50 (22.4)                     | 40 (13.1)                                | 0.004   |
| Interval time between study and data collection (year)a | 5.7 ± 2.9 | 6.0 ± 3.0 | 0.887   |

Abbreviations: BMI, body mass index; GA, gestational age.
aData given as mean ± SD.
bData given as n (%).
There have been consistent reports on the lowered risk of preterm birth after ER in previous studies, and the results of the current study also show an increased risk of preterm birth in the MFPR group.

were higher in the EM group than in the MFPR group, and (4) the risk of developmental delay was lower in the EM group than in the MFPR group.

### TABLE 2 Obstetric outcomes

| Outcome                                      | Expectant management (n = 225) | Multifetal pregnancy reduction (n = 327) | Unadjusted odds ratio (95% CI) (Reference: Expectant management) | Adjusted odds ratio (95% CI) (Reference: Expectant management) | p value |
|----------------------------------------------|-------------------------------|----------------------------------------|-----------------------------------------------------------------|-----------------------------------------------------------------|---------|
| Loss of all the fetuses before 23 weeksb     | 2 (0.9)                       | 21 (6.4)                               | 7.65 (1.78–32.97)                                               | 14.87 (1.89–117.04)                                             | 0.010   |
| Pregnancies with                             |                               |                                        |                                                                 |                                                                 |         |
| No survivorsb                                 | 5 (2.2)                       | 26 (8.0)                               | 3.80 (1.44–10.05)                                               | 5.87 (1.66–20.73)                                              | 0.006   |
| One survivorb                                 | 2 (0.9)                       | 30 (9.2)                               |                                                                  |                                                                 |         |
| Two survivorsb                                | 12 (5.3)                      | 271 (82.9)                             |                                                                  |                                                                 |         |
| Three survivorsb                              | 206 (91.6)                    | –                                      | 0.26 (0.10–0.70)                                               | 0.17 (0.05–0.60)                                              | 0.006   |
| At least one survivorb                        | 220 (97.8)                    | 301 (92.0)                             |                                                                  |                                                                 |         |
| Delivery outcomes ≥23 weeks                   |                               |                                        |                                                                 |                                                                 |         |
| GA at delivery (week)c                       | 33.8 ± 2.8                    | 35.5 ± 2.6                             |                                                                  |                                                                 |         |
| Preterm birth                                 |                               |                                        |                                                                 |                                                                 |         |
| 23–27+6 weeksb                                | 11/223 (4.9)                  | 4/306 (1.3)                            | 0.26 (0.08–0.81)                                               | 0.29 (0.08–1.00)                                              | 0.050   |
| 23–31+6 weeksb                                | 33/223 (14.8)                 | 20/306 (6.5)                           | 0.40 (0.22–0.72)                                               | 0.40 (0.21–0.76)                                              | 0.005   |
| 23–33+6 weeksb                                | 71/223 (31.8)                 | 48/306 (15.7)                          | 0.40 (0.26–0.61)                                               | 0.47 (0.30–0.73)                                              | 0.001   |
| 23–35+6 weeksb                                | 211/223 (94.6)                | 103/306 (33.7)                         | 0.03 (0.02–0.05)                                               | 0.03 (0.02–0.06)                                              | <0.001  |
| Pregnancy with                                |                               |                                        |                                                                 |                                                                 |         |
| Preeclampsiaab                                | 30 (13.3)                     | 17 (5.2)                               | 0.36 (0.19–0.66)                                               | 0.29 (0.15–0.56)                                              | <0.001  |
| Gestational diabetesb                         | 14 (6.2)                      | 11 (3.4)                               | 0.53 (0.23–1.18)                                               | 0.48 (0.20–1.12)                                              | 0.100   |
| Postpartum hemorrhagab                        | 5 (2.2)                       | 15 (4.6)                               | 2.12 (0.76–5.91)                                               | 1.84 (0.63–5.36)                                              | 0.261   |

Abbreviation: GA, gestational age.

a All outcomes were adjusted for maternal age, body mass index and method of conception.
b Data given as n (%).
c Data given as mean ± SD.

d Data given as mean ± SD.

### TABLE 3 The effect of expectant management on survival and perinatal outcomes

| Outcome                                      | Expectant management (N = 675) | Multifetal pregnancy reduction (N = 654) | Unadjusted odds ratio (95% CI) (Reference: Expectant management) | Adjusted odds ratio (95% CI) (Reference: Expectant management) | p value |
|----------------------------------------------|-------------------------------|----------------------------------------|-----------------------------------------------------------------|-----------------------------------------------------------------|---------|
| Survival                                     |                               |                                        |                                                                 |                                                                 |         |
| Live birthd                                   | 665 (97.0)                    | 580 (88.7)                             | 0.13 (0.06–0.31)                                               | 0.09 (0.03–0.30)                                              | <0.001  |
| Survival during 2 h after birthd             | 649 (96.1)                    | 579 (88.5)                             | 0.31 (0.20–0.49)                                               | 0.28 (0.16–0.49)                                              | <0.001  |
| Survival to discharge                        | 644 (95.4)                    | 572 (87.5)                             | 0.34 (0.22–0.52)                                               | 0.30 (0.18–0.49)                                              | <0.001  |
| Neonatal outcomes                            |                               |                                        |                                                                 |                                                                 |         |
| Birthweight (g)e                             | 1874 ± 443                    | 2318 ± 500                             |                                                                  |                                                                 |         |
| Gestational age at birth (week)e             | 33.8 ± 2.4                    | 35.6 ± 2.4                             |                                                                  |                                                                 |         |
| Apgar score at 5 min <7d                     | 46/646 (7.1)                  | 24/580 (4.1)                           | 0.56 (0.34–0.94)                                               | 0.65 (0.37–1.14)                                              | 0.133   |

a Analyzed with GEE.
b All outcomes were adjusted for maternal age, body mass index, method of conception, steroids, magnesium sulfate and antibiotics.
c Cases with fetal loss before 23 weeks were excluded.
d Data given as n (%).
e Data given as mean ± SD.
However, whether the risk of nonviable pregnancy loss (miscarriage) after ER is increased is controversial. In a recent meta-analysis of six studies, the miscarriage risk was not different between the EM and MFPR groups. In the MFPR group compared with the EM group, two studies (Antsaklis et al., n = 255; Chaveeva et al., n = 494) showed increased miscarriage rates (from 2.9% to 8.1% and

**FIGURE 1** Survival curve for gestational age at birth or at which intrauterine death was diagnosed between the expectant management group (blue line) and multifetal pregnancy reduction group (green line). Note higher rates of ongoing pregnancies before 32 weeks of gestation in expectant management group than multifetal pregnancy reduction group.

**TABLE 4** The effect of expectant management on postnatal morbidities

| Morbidity during hospitalization<sup>c</sup> | Expectant management | Multifetal pregnancy reduction | Unadjusted odds ratio (95% CI) (Reference: Expectant management) | p value<sup>a</sup> | Adjusted odds ratio (95% CI) (Reference: Expectant management) | p value<sup>a</sup> |
|------------------------------------------|----------------------|-------------------------------|----------------------------------------------------------------|-----------------|----------------------------------------------------------------|-----------------|
| Neonatal sepsis<sup>e</sup>             | (n = 631)            | (n = 577)                     | 3.17 (1.53–6.58)                                                 | 0.002           | 3.62 (1.82–7.21)                                                 | <0.001           |
| Intracerebral hemorrhage<sup>e</sup>    | 10 (1.6)             | 28 (4.9)                      | 1.50 (0.69–3.30)                                                 | 0.309           | 1.76 (0.74–4.21)                                                 | 0.205           |
| Retinopathy of prematurity<sup>e</sup>  | 22 (3.5)             | 26 (4.5)                      | 1.30 (0.73–2.32)                                                 | 0.372           | 2.28 (1.09–4.74)                                                 | 0.028           |
| Patent ductus arteriosus<sup>e</sup>   | 66 (9.7)             | 24 (4.2)                      | 0.41 (0.25–0.66)                                                 | <0.001          | 0.48 (0.28–0.82)                                                 | 0.007           |
| Respiratory distress syndrome<sup>e</sup> | 84 (13.3)           | 72 (12.5)                     | 0.93 (0.66–1.30)                                                 | 0.666           | 1.74 (1.07–2.82)                                                 | 0.024           |
| Bronchopulmonary dysplasia<sup>e</sup> | 23 (3.7)             | 4 (0.7)                       | 0.18 (0.06–0.54)                                                 | 0.002           | 0.20 (0.07–0.62)                                                 | 0.005           |
| Necrotizing enterocolitis<sup>e</sup>  | 5 (0.8)              | 3 (0.5)                       | 0.65 (0.16–2.75)                                                 | 0.563           | 0.77 (0.16–3.73)                                                 | 0.743           |
|Composite morbidity<sup>d,e</sup>      | 108 (17.1)           | 93 (16.1)                     | 0.93 (0.69–1.26)                                                 | 0.642           | 1.43 (0.96–2.13)                                                 | 0.079           |

| Morbidity at present<sup>d</sup>       | (N = 617)            | (N = 544)                     |                                                                  |                 |                                                                  |                 |
|----------------------------------------|----------------------|-------------------------------|----------------------------------------------------------------|-----------------|----------------------------------------------------------------|-----------------|
| Developmental delay<sup>e</sup>        | 14 (2.3)             | 24 (4.4)                      | 1.99 (1.02–3.88)                                                 | 0.044           | 2.89 (1.38–6.02)                                                 | 0.005           |
| Cerebral palsy<sup>e</sup>             | 4 (0.6)              | 10 (1.8)                      | 2.87 (0.90–9.20)                                                 | 0.076           | 3.79 (1.00–14.41)                                                | 0.050           |

<sup>a</sup> Analyzed with GEE.

<sup>b</sup> All outcomes were adjusted for maternal age, body mass index, method of conception, steroids, magnesium sulfate and antibiotics.

<sup>c</sup> Cases with fetal loss before 23 weeks, cases with neonatal death within 2 h after birth, or cases whose medical records were not available were excluded.

<sup>d</sup> Composite morbidity during hospitalization includes neonatal sepsis, intracerebral hemorrhage, retinopathy of prematurity, patent ductus arteriosus, pulmonary hypertension, respiratory distress syndrome, bronchopulmonary dysplasia and necrotizing enterocolitis.

<sup>e</sup> Data given as n (%)

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from 3.9% to 7.9%, respectively,\textsuperscript{12,15} two studies (Drugan et al.\textsuperscript{16} n = 82; Shiva et al.\textsuperscript{13} n = 115) showed a similar miscarriage rate (from 5.6% to 6.5% and from 12.3% to 12.1%, respectively,\textsuperscript{13,16} and two studies (Ata et al.\textsuperscript{17} n = 65; Skiadas et al.\textsuperscript{18} n = 156) showed decreased miscarriage rates (from 17.9% to 7.7% and from 14.5% to 6.9%, respectively,\textsuperscript{17,18}) Higher miscarriage rates in the MFPR group have been observed in studies with larger numbers of subjects.\textsuperscript{12,15} Their results are consistent with the current study. With increased clinical experience of the MFPR practice, it has been reported that the miscarriage risk after MFPR of triplet to twin pregnancies has decreased and reached the twins’ natural miscarriage rate.\textsuperscript{19,20} However, considering that less invasive procedures such as chorionic villus sampling or amniocentesis also have procedure-related fetal loss,\textsuperscript{21} it is not reasonable that MFPR is totally innocuous. We are concerned that the dead fetus may have both acute and remote effects on the remaining live fetuses.

In the current study, we showed a statistically significant difference in the rate of pregnancies with at least one live neonate in the EM group (97.8%) compared with that in the MFPR group (92.0%) (p = 0.002). This result may serve as a valuable information for the pregnant woman and her family who consider MFPR. In terms of at least one survivor, women keeping all three fetuses (EM group) have better outcomes than women sacrificing one fetus (MFPR group). Ninety-seven percent of at least one survivor seems to be a high number. However, 94.8% of at least one survivor had already been reported in one study, which was conducted from 1986 to 2013.\textsuperscript{22} Considering that the current study was conducted more recently, it might have been expected that the outcome of our study would be better. The fact that at least one survival rate in the MFPR group was lower despite the sacrifice of one-third of the fetuses may affect the attitude toward MFPR.

We tried to determine whether survival and postnatal outcomes differed according to the methods of MFPR (ER vs FR). There was no evidence of difference between the two methods with respect to nonviable fetal loss before 23 weeks of gestation. However, the rate of preterm delivery before 36 weeks of gestation was higher in the ER group (31 [43.1%] vs 72 [30.8%], p = 0.038) (Table S3). We also analyzed survival and postnatal outcomes according to the indications for MFPR. There was no significant difference between cases with elective MFPR and cases with selective MFPR due to fetal status (Table S4).

What is interesting in this study is that the risk of neonatal sepsis was significantly higher in the MFPR group than in the EM group even after multivariable analysis. This result suggests that MFPR itself might be a risk factor for sepsis. We suggest that a clinical or subclinical inflammatory response to the dead fetal and placental tissue following MFPR might result in the release of cytokines, which may make the surviving fetus more fragile to septic conditions.

The results on long-term neurodevelopmental outcomes are the major strengths of the current study. Although prolonged gestation and increase in birthweight are also meaningful, more critical outcomes are long-term sequelae such as developmental delay and CP. We showed that the risk of developmental delay in surviving neonates was lower in the EM group, even though the rate of early preterm birth was significantly higher in the EM group than that in the MFPR group. The incidence of CP in triplet pregnancy was 28–44.8/1000, based on data from the 1980s,\textsuperscript{23–25} but it decreased to 18/1000 based on the data from the 1990s and the early 2000s.\textsuperscript{22} Actually, the risk of CP is highest in neonates delivered at less than 28 weeks of gestation. It was recently reported that the rate of CP was 5.6% (21/381) in triplets or higher-order births of extremely low birthweight infants.\textsuperscript{26} This study revealed much lower rates of CP, only 0.4% in the EM group and 2.0% in the MFPR group, because only a small number of cases in the current study belonged to the extremely low birthweight group. Moreover, after the introduction of magnesium sulfate for neuroprotection in threatened early preterm delivery,\textsuperscript{27,28} CP incidence is expected to decrease further in the near future.

In the MFPR group, developmental delay or CP occurred even though the fetuses were born after 34 weeks of gestation and had no neonatal complications (Table S5). Most of the studies on the outcomes of MFPR reported short-term pregnancy outcomes, but not long-term outcomes related to neurodevelopment. In multifetal pregnancy with different chorionicity, injection of potassium chloride into the heart of one fetus has been considered a safe method that does not affect the remaining fetus;\textsuperscript{29} however, there are no reports on the long-term prognosis of the remaining fetuses after this procedure. There seems to be a possibility that the remaining fetuses may have neurological damage after this procedure and then develop into developmental delay or CP several years after birth. In the future, long-term observations of these children are needed, as well as animal experiments to reveal their pathophysiology.

The other strength of the study is that it was conducted with a large number of trichorionic pregnancies. We were able to study a significantly higher number of trichorionic pregnancy cases compared with other previous studies.

However, our study had several limitations. First, this was a retrospective cohort study design. Second, we could not evaluate developmental delays using an identical method for all children. Third, there were some missing data because information was collected from previously written medical records.

## 5 Conclusion

In conclusion, the possibility of EM to improve survival and reduce the risk of developmental delay has been shown compared with MFPR in trichorionic triplet pregnancies. Postnatal short- and long-term outcomes in trichorionic triplets were improved under recent obstetric and neonatal care. To our knowledge, this is the first report in which neurodevelopmental long-term outcomes were compared between the EM group and the MFPR group in trichorionic triplet pregnancies.

### Author Contributions

JYL: study design, acquisition of data, statistical analysis, data interpretation, and writing. SML: statistical analysis, data interpretation,
and writing. MJ: data acquisition and statistical analysis. SO: statistical analysis and data interpretation. SH and SAC: data acquisition of and statistical analysis. JKJ: study design, data acquisition, statistical analysis, data interpretation, and writing.

CONFLICT OF INTEREST

None.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher’s website.

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