Short-term and long-term outcomes of expectant management compared to embryo reduction to a twin pregnancy in women with triplet pregnancy: a retrospective cohort study

Ji Yeon Lee[1], Seung Mi Lee[2], Mina Jeong[2], Sohee Oh[3], Subeen Hong[2], and Jong Kwan Jun[2]

[1]CHA Bundang Medical Center, CHA University School of Medicine
[2]Seoul National University College of Medicine
[3]Seoul National University Seoul Metropolitan Government Boramae Medical Center

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Abstract

Objective: To compare maternal, perinatal and long-term outcome of triplet pregnancies managed expectantly with those reduced to twins Design: A retrospective cohort study Setting: Tertiary medical institutions in South Korea Population: We examined short-term and long-term outcomes in 524 triplet pregnancies with three live fetuses before 14 weeks of gestation that were comprised of expectant management(EM) group (n=213) and embryo reduction(ER) group (n=311) from 2006 to 2017. Methods: The two groups were compared for the following outcomes. Main Outcome Measures: 1) the rates of non-viable pregnancy loss before 23 weeks, 2) the rates of preterm birth before 32 weeks of gestation; 3) the number of survival fetuses; and 4) long term neurodevelopmental outcomes. Results: In the EM group, the risk of preterm delivery (<36, <34, <32, and <28 weeks) was higher compared to the ER group. However, the risk of non-viable pregnancy loss was lower [2(0.9%) vs. 20(6.4%), p=0.008] in EM group, and the rate of cases with at least one alive neonate were higher in EM group than ER group [208(97.7%) vs. 287(92.3), p=0.013]. The survival rate until discharge of neonates were also significantly higher in the EM group than the ER group [607(95.0%) vs. 545(87.6), p=0.001]. The risk of developmental delay or cerebral palsy in survived neonates was not different between the two groups of cases. Conclusions: In triplet pregnancies, EM may improve the chance of fetal survival, without any significant differences in developmental delay and cerebral palsy.

Introduction

Advanced maternal age and widely application of assisted reproductive technologies 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.[1] It is well known that multiple gestation is associated with an increased risk of maternal complications, as well as high perinatal morbidity and mortality.[2]

Because triplet or higher-order multiple gestation are more likely to develop these risks, several preventive strategies to limit the number of fetuses are suggested. Elective single embryo transfer (eSET) and multifetal pregnancy reduction (MFPR) are the recommended methods for this purpose. In contrast to eSET which is a relatively acceptable useful method,[3,4] MFPR is a more complicated method in clinical practice, involving a number of medical, economical, 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 evidences are required to recommend MFPR in triplet pregnancy. Most data to advocate MFPR in triplet pregnancy were derived from comparison of maternal and perinatal outcomes between twin and triplet pregnancies, although direct comparison of

outcomes between continuing triplets and reduced twin from triplets is more desirable. To show the usefulness of MFPR for triplet pregnancy, improved maternal and neonatal morbidity and mortality in reduced twin from triplets should be demonstrated, but few studies have been conducted in 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.[5,6] Nonetheless, there are conflicting data about whether pregnancies reduced from triplets to twins fare better than expectantly managed triplet pregnancies.[7] Moreover, most of studies were conducted several years or decades ago. Maternal and fetal morbidity and mortality should be carefully assessed on the basis of contemporary data. To clarify this issue, we conducted this study to compare maternal, perinatal and long-term outcome of triplet pregnancies managed expectantly with those reduced to twins.

Materials and Methods

We performed a retrospective cohort study from January 2006 to August 2017. We identified all triplet pregnancies which underwent first trimester ultrasonography to measure the fetal crown-rump length and to determine amnionicity and chronicity. Only trichorionic triamniotic triplet pregnancies were included, and were divided into two groups according to their decisions after counseling on the MFPR; expectant management (EM) group consisting of women who declined MFPR and embryo reduction (ER) group consisting of women who chose MFPR from triplet to twin pregnancy. Women who decided to reduce to singleton pregnancy from triplet pregnancy were excluded. The institutional review boards of Seoul National University Hospital Clinical Research Institute (IRB No.; H-1311-045-533) and CHA Bundang Medical Center approved this study (IRB No.; C 2016-10-007).

MFPR were performed with transvaginal or transabdominal intrathoracic potassium chloride injection before 14 weeks of gestation. We reviewed the clinical records of the mothers and babies for information concerning maternal demographics, clinical presentation, laboratory examinations, ultrasound assessments, and birth outcome. The two groups were compared for the rates of non-viable 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.

To evaluate the short-term birth outcome, we investigated neonatal survival and composite morbidity, which was defined as the occurrence of at least one of the followings: neonatal sepsis, intracranial hemorrhage (ICH), retinopathy of prematurity (ROP), patent ductus arteriosus (PDA), pulmonary hypertension, respiratory distress syndrome (RDS), bronchopulmonary dysplasia (BPD), and necrotizing enterocolitis (NEC). We evaluated SGA using the standard described in the previous report.[8] We investigated the long-term neurodevelopment outcomes after one year of corrected age. Developmental delay and cerebral palsy were evaluated by the Korean Ages and Stages Questionnaire (K-ASQ), or Gross Motor Function Measure (GMFM) or chart review. Because the K-ASQ is useful only for young children (4-60 months of age), older children (preschool or elementary school age) were instead evaluated by pediatric charts regarding their ability to perform daily activities or learning ability in school. We considered development to be normal in children described with no difficulties in fulfilling their normal academic obligations; those who attended special schools for mentally retarded children were categorized as cases of developmental delay.

Statistical analysis was performed using SPSS version 23.0 (SPSS Institute, Chicago, IL, USA) and R, version 3.3.1 software (R Foundation for Statistical Computing, Vienna, Austria; http://www.r-project.org). We analyzed discrete data using Fisher's exact test and comparisons of continuous variables were performed with Mann-Whitney U test, as appropriate. A generalized estimating equation (GEE) was used to assess which variables were associated with neonatal outcomes, accounting for the familial correlation in the model, because the study population consisted of twin or triplet pairs within a single mother.[9] We also performed a multivariable analysis including maternal age, BMI and method of conception as covariates, which were selected with $p < 0.2$ in univariate analysis when comparing cases with neonatal survival or those with neonatal death. A P value <0.05 was considered statistically significant.

Results

After excluding monochorionic or dichorionic triplets, we identified 524 trichorionic triplet pregnancies which included 213 cases in expectant management (EM) group and 311 cases in embryo reduction (ER) group.

Table 1 shows the clinical characteristics of the study population. There were no differences in the mean maternal age and body mass index and the frequency of nulliparity and history of previous preterm birth between two groups. There were more cases becoming pregnant after in vitro fertilization (IVF) in the ER group than in the EM group.

Table 2 compares the obstetric outcomes between the two groups of cases. In the EM group, the risk of preterm delivery (<36, <34, <32, and <28 weeks) was higher compared to the ER group. However, in EM group, the risk of non-viable pregnancy loss was lower [2(0.9%) vs. 20(6.4%), p=0.008] that in ER group. Moreover, the rate of cases with at least one alive neonate were higher [208(97.7%) vs. 287(92.3%), p=0.013]. In terms of obstetric complications, the risk of preeclampsia was higher in EM group than in ER group [27 (12.8%) vs. 16 (5.5%), p<0.05], whereas the risk of gestational diabetes and postpartum hemorrhage was not different between the two groups. Even after adjustment for maternal age, BMI, and method of conception, the risk of non-viable fetal loss and the rate of no neonatal survivor were significantly lower in EM, whereas the risk of preterm delivery and preeclampsia was higher in EM than in ER group.

The study population included 1,261 fetuses: 639 in the EM group and 622 in the ER group (Table 3). The survival rate during 2 hours after birth [612(95.8%) vs. 552(88.7), p=0.001] and the survival rate until discharge of neonates were also significantly higher in the EM group than the ER group [607(95.0%) vs. 545(87.6), p=0.001]. The rate of neonates who admitted to NICU was higher in ER group [313(50.4%) vs. 201(36.3), p<0.001], but the risk of neonatal composite morbidity during hospitalization was not different between the two groups [113(19.1% vs. 105 (20.0%), p=NS). The risk of PDA and BPD was higher in EM group, but the risk of neonatal sepsis was lower in EM group [10(1.7%) vs. 27(5.1), p=0.017].

We evaluated the risk of developmental delay and cerebral palsy in 958 babies. The risk of developmental delay and cerebral were not significantly different between the two groups both in the univariable and multivariable analyses.

Discussion

The principal findings of the current study are as follows: 1) the risk of preterm birth was higher in EM group compared to ER group; 2) however, the risk of non-viable pregnancy loss lower in EM group than in ER group; 3) the rate of cases with at least one alive neonate was higher in EM group compared to ER group; 4) short- and long-term outcome of neonates was comparable between ER and EM groups.

The risk of preterm birth had been consistently reported to be lowered after ER in previous studies, and the result of the current study also shows increased risk of preterm birth in ER group.[7,10,11] However, the risk of non-viable pregnancy loss (miscarriage) after ER is controversial. In recent meta-analysis which analyzed 6 studies, the miscarriage risk was not different between EM and ER groups.[12] In ER group compared to EM group, two studies [Antsaklis et al, 2004 (n=255); Chaveeva et al, 2013 (n=494)] showed increased miscarriage rate (2.9% ->8.1%; 3.9%->7.9% respectively),[10,13] two studies [Drugan et al, 2013 (n=82); Shiva et al, 2014 (n=115)] showed similar rate (from 5.6% to 6.5%; from 12.3% to 12.1% respectively),[11,14] and two studies [Ata et al., 2011 (n=65); Skiadas et al., 2011 (n=156)] showed decreased miscarriage rate (from 17.9% to 7.7%; from 14.5% to 6.9% respectively).[15,16] Higher miscarriage rates in ER group have been observed in studies with larger numbers of subjects.[10,13] Their results are consistent with the current study. As experience of MFPR increases, it was reported that the miscarriage risk after MFPR of triplet to twin pregnancies has reached to the twin's natural miscarriage rate.[17,18] However, considering that less invasive procedures such as chorionic villi sampling or amniocentesis has procedure related fetal loss,[19] it is not reasonable that MFPR is innocuous. And we are concerned that dead fetus may have acute and remote effects on the other living fetuses.

In the current study, we have shown a statistically significant difference in the rate of pregnancies with at least one alive neonate in the EM group (97.7%) compared to the ER group (92.3%) (p=0.013). This result may

be important information for pregnant woman and her family who consider MFPR. In term of at least one survival, women with keeping all three fetuses (EM group) have better outcome than women with sacrificing one fetus (ER group). Ninety-seven percent of at least one survival seems to be high. However, 94.8% of at least one survival was already reported in one study which was conducted from 1986 to 2013[13]. Considering that current study was done more recently, better outcomes of the current study is not unexpected. Even though one third of fetuses are already sacrificed in ER group, lower rate of at least one survival in ER may have an effect on the attitude to MFPR.

What is interesting in this study is that the risk of neonatal sepsis was significantly higher in the ER group compared with the EM group even after multivariable analysis. This result suggests that ER itself might be a risk factor for sepsis. We think that there is a possibility that a clinical or subclinical inflammatory response to the dead fetal and placental tissue following embryo reduction might result in release of cytokines which may affect the survived fetus more fragile to septic condition.

The results on long-term neurodevelopmental outcomes are the major strength of the current study. Although prolonged gestation and increase in birth weight are also meaningful, more critical outcomes are long-term sequelae such as cerebral palsy (CP) and developmental delay. We showed rates of developmental delay and cerebral palsy which were not different between the EM group and ER group even though the rate of early preterm birth was significantly higher in the EM group. The incidence of CP in the triplet pregnancy was 28 to 44.8 / 1000, based on data from the 1980s and, [20-22] but it decreased to 18/1000 on the data from 1990s and early 2000s.[23]Actually, the risk of cerebral palsy 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 birth weight infants.[24] Our study revealed much lower rates of CP as only 0.44% in EM group and 2.0% in ER group. Moreover, after introduction of MgSO4 for neuroprotection in threatened early preterm delivery,[25,26] CP incidence will decrease further in the near future.

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 patients, due to the wide range of age at the time of examination.

Conclusion

In conclusion, expectant management may improve the chance of fetal survival compared to embryo reduction in triplet pregnancies. And there were no significant differences in developmental delay and CP between the EM group and the ER group in this study. To our knowledge, this is the first report in which neurodevelopmental long-term outcomes were compared between EM group and ER group in triplet pregnancies.

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Disclosure of interests

None of the authors has any potential conflict of interest.

Contribution to authorship

JYL participated in design of the study, acquisition of data, statistical analysis, interpretation of data, writing of manuscript, revision of manuscript. SML participated in statistical analysis, interpretation of data, writing of manuscript, revision of manuscript. MJ participated in acquisition of data, statistical analysis, revision of manuscript. SO participated in statistical analysis, interpretation of data, revision of manuscript. SH participated in acquisition of data, statistical analysis, revision of manuscript. JKJ participated in design of study, acquisition of data, statistical analysis, interpretation of data, writing of manuscript, revision of manuscript.

Ethics approval

The institutional review boards of Seoul National University Hospital Clinical Research Institute (IRB No.; H-1311-045-533) and CHA Bundang Medical Center approved this study (IRB No.; C 2016-10-007).

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Table 1. Clinical characteristics of the study population

Characteristic	Expectant management (N=213)	Embryo reduction (N=311)	p-value
Maternal age (y)*	33.2 ± 3.4	33.4 ± 3.9	NS
Height (cm)*	162.0 ± 5.4	161.4 ± 5.3	NS
BMI*	22.0 ± 3.4	21.7 ± 3.4	NS
Nulliparity^{+}	182 (85.4)	264 (84.9)	NS
Prior preterm birth^{+}	2 (0.9)	8 (2.6)	NS
Method of conception			<0.001
Spontaneous^{+}	9 (4.2)	12 (3.9)	
Ovarian hyperstimulation^{+}	89 (41.8)	43 (13.8)	
In vitro fertilization^{+}	115 (54.0)	256 (82.3)	

BMI, body mass index; NS, not significant

*Data given as mean ± SD, $^{+}$Data given as n (%)

Table 2. Obstetric outcomes

	Expectant management (n=213)	Embryo reduction (n=311)	Unadjusted odds ratio (95% CI) (Reference: embryo reduction)	p-value	Adjusted odds ratio (95% CI)	p-value[b]
Nonviable fetal loss <23 week*	2 (0.9)	20 (6.4)	0.14 (0.03-0.60)	0.008	0.08 (0.01-0.65)	0.017
Pregnancies with						
No survivors*	5 (2.3)	24 (7.7)				
One survivor*	2 (0.9)	29 (9.3)				
Two survivors*	12 (5.6)	258 (83.0)				
Three survivors*	194 (91.1)	–				
At least one survivor*	208 (97.7)	287 (92.3)	3.48 (1.31-9.27)	0.013	4.54 (1.31-15.70)	0.017
Delivery outcomes [?]	(N=211)	(N=291)				
23 week						
GA at delivery (week)[+ a]	33.8 ± 2.6	35.7 ± 2.4				
Preterm birth						
23-27+6 week*	11 (5.2)	4 (1.4)	3.95 (1.24-12.57)	0.020	3.52 (1.02-12.17)	0.047
23-31+6 week*	35 (16.6)	19 (6.5)	2.85 (1.58-5.14)	0.001	2.88 (1.51-5.48)	0.001
23-33+6 week*	70 (33.2)	44 (15.1)	2.79 (1.81-4.29)	<0.001	2.43 (1.51-3.91)	<0.001
23-35+6 week*	199 (94.3)	94 (32.3)	34.75 (18.47-65.41)	<0.001	33.26 (17.14-64.54)	<0.001
Pregnancies with						
Preeclampsia*	27 (12.8)	16 (5.5)	2.52 (1.32-4.81)	0.005	3.14 (1.56-6.31)	0.001
Gestational diabetes*	12 (5.7)	10 (3.4)	1.69 (0.72-4.00)	NS	1.74 (0.66-4.54)	NS
Postpartum hemorrhage*	5 (2.4)	15 (5.2)	0.45 (0.16-1.25)	NS	0.56 (1.19-1.64)	NS

GA, gestational age; NS, not significant;

*Data given as n (%), [+]Data given as mean ± SD

[a] mean gestational age was used in cases with delayed delivery, [b]All outcomes were adjusted for age, BMI,

and method of conception

Table 3. Neonatal outcomes and the effect of expectant management on survival and postnatal morbidities

Outcome	Expectant management (N=639)	Embryo reduction (N=622)	Unadjusted odds ratio (95% CI)	p-value [c]	Adjusted odds ratio (95% CI)	p-value [c]
Survival[c]						
Survival during 2 hours after birth*	612 (95.8)	552 (88.7)	2.87 (1.54-5.37)	0.001	3.13 (1.57-6.22)	0.001
Survival to discharge*	607 (95.0)	545 (87.6)	2.68 (1.49-4.82)	0.001	2.82 (1.46-5.44)	0.002
Neonatal characteristics[a]	(N=632)	(N=564)				
Gender (male) *	324/616 (52.6)	291/560 (53.5)				
Birth weight (gram) +	1851 ± 472	2307 ± 545				
Apgar score at 5min <7*	52/623 (8.3)	33/563 (5.9)	1.47 (0.84-2.57)	0.176	1.70 (0.96-3.01)	0.067
NIUC admission*	313/621 (50.4)	201/553 (36.3)	1.83 (1.32-2.53)	<0.001	1.58 (1.12-2.24)	0.010
Morbidity during hospitalization[b]	(N=593)	(N=526)				
Neonatal sepsis*	10 (1.7)	27 (5.1)	0.32 (0.13-0.82)	0.017	0.36 (0.16-0.76)	0.009
Intracerebral hemorrhage*	11 (1.9)	15 (2.9)	0.61 (0.21-1.77)	0.364	0.79 (0.29-2.16)	0.645
Retinopathy of prematurity*	26 (4.4)	35 (6.7)	0.67 (0.33-1.37)	0.272	0.66 (0.30-1.41)	0.282
Patent ductus arteriosus*	65 (11.0)	23 (4.4)	2.57 (1.40-4.70)	0.002	2.63 (1.39-5.00)	0.003
Pulmonary hypertension*	8 (1.3)	1 (0.2)	6.08 (0.72-51.62)	0.098	6.91 (1.51-65.49)	0.019
Respiratory distress syndrome*	86 (14.5)	85 (16.2)	0.88 (0.57-1.36)	0.566	0.92 (0.56-1.51)	0.741
Bronchopulmonary dysplasia*	26 (4.4)	4 (0.8)	6.56 (1.69-25.51)	0.007	4.23 (1.59-13.86)	0.006
Necrotizing enterocolitis*	5 (0.8)	3 (0.6)	1.42 (0.31-6.61)	0.654	1.65 (0.41-7.47)	0.441
Composite morbidity during hospitalization*	113 (19.1)	105 (20.0)	0.94 (0.64-1.39)	0.763	0.96 (0.62-1.49)	0.844
Morbidity at present	(N=451)	(N=507)				

Outcome	Expectant management (N=639)	Embryo reduction (N=622)	Unadjusted odds ratio (95% CI)	p-value [c]	Adjusted odds ratio (95% CI)	p-value [c]
Developmental delay*	9 (2.0)	20 (3.9)	0.50 (0.20-1.27)	0.147	0.47 (0.20-1.11)	0.087
Cerebral palsy*	2 (0.4)	10 (2.0)	0.22 (0.05-1.03)	0.055	0.41 (0.08-1.45)	0.179

SGA, small for gestational age; NICU, neonatal intensive care unit, NS, not significant

[a] cases with fetal loss before 23 weeks were excluded[b] cases with fetal loss before 23 weeks, cases with neonatal death within 2 hours after birth, or cases whose medical records were not available were excluded

[c] analyzed with GEE

All outcomes were adjusted for maternal age (y), body mass index, and method of conception.

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.

*Data given as n (%), +Data given as mean ± SD