

A case series of higher-order multifetal pregnancies managed at a tertiary maternity unit

Dear Editor,

Delayed childbearing and increased use of assisted reproduction technology (ART) have resulted in a dramatic rise in the incidence of multifetal pregnancies. In 2022, the incidence of twin birth was 1 in 38.2 (932 live births) and triplet birth 1 in 1978 (18 live births) in Singapore.¹ Preterm birth and its associated complications remain the most significant risks of multifetal pregnancies—60.5% of twins and 100% of triplets were born <37 weeks in Singapore in 2019. The relative risks of cerebral palsy in triplets and twins compared with singletons are 12.7 and 4.9, respectively.²

A Cochrane review reported that multifetal pregnancy reduction (MFPR) is associated with a reduction in pregnancy loss, antenatal complications, birth before 36 weeks, low birth weight and neonatal death. However, the evidence was drawn from non-randomised studies.³ Skilled management of multifetal pregnancies is crucial in contemporary obstetrical practice. This study aims to compare the outcomes of multifetal pregnancies with and without fetal reduction (FR).

This is a retrospective cohort study of patients with higher-order pregnancies managed at the National University Hospital, Singapore, between January 2014 to April 2019. Ethics approval from Domain Specific Review Board and waiver of patient consent was obtained. Data on demographics, antenatal and neonatal complications were retrieved from electronic medical records.

Descriptive statistics were used to report pregnancy and neonatal outcomes. Continuous variables were reported as mean and standard deviation, and analysed with sample Student's t-test. Categorical variables were reported as frequency (percentage) and were analysed by chi-square test. A *P* value of <0.05 was taken as statistically significant.

After confirmation of a higher-order pregnancy at a first trimester dating scan, women will be seen by experienced fetal medicine specialists and counselled on all 3 possible options: expectant management, MFPR to twins or singleton, or the least desirable option of termination of pregnancy.

Women who choose MFPR will be thoroughly counselled on the risks of MFPR procedure, including risks of reducing to monochorionic (MC) twins. Structural abnormalities in either fetus, patient's preference for a singleton or twin pregnancy, accessibility, and distance from the cervix were some factors considered. In our study, all FR procedures were done with potassium chloride injection. Following the procedure, patients were reviewed within 1 week and followed up at the high-risk pregnancy clinic.

Women who choose expectant management will also be followed up closely in the high-risk pregnancy clinic with frequent scans—2 weekly for amniotic fluid volume and umbilical artery doppler assessments and 4 weekly for growth estimation.

A total of 24 higher-order pregnancies were included: 91.6% (22/24) triplet pregnancies and 8.4% (2/24) quadruplet pregnancies. Of these, 91.6% (22/24) were conceived via ART procedures and 16.7% (2/24) were spontaneously conceived; 54.1% (13/24) opted for expectant management and 45.8% (11/24) underwent FR. Both cases of quadruplet pregnancies underwent FR to twins. Fourteen higher-order pregnancies were excluded as they were lost to follow-up.

Of the 11 MFPR cases, 8/11 (73%) were reduced to dichorionic twins, 2/11 (18%) to MC twins and 1/11 (8.1%) to a singleton. The pregnancy that was reduced to a singleton was initially a dichorionic diamniotic triplet (1 monochorionic monoamniotic twin and a separate singleton).

Table 1 summarises pregnancy and neonatal outcomes. The results show that FR prolongs pregnancy and reduces the risk of preterm birth <30 weeks. The gestational age (GA) at delivery was significantly higher in the FR group—34.2 weeks in the expectant management group versus 36.3 and 40 weeks in the FR to twins and singleton, respectively (*P*=0.014). When GA was examined as a categorical outcome, the FR group was more likely to deliver >30 weeks compared with the expectant management group (*P*=0.018). The risk of preterm birth <32–33 weeks following FR has been reported to be between 24% and 37%.^{4–6} In our study, a lower rate of 20% in the FR group delivered between 30–34 weeks. The mean birth weight in the FR to twin group was 1073 g, higher than that in the expectant management group (*P*<0.05).

A later GA at delivery also correlates with improvement in neonatal outcomes.^{7,8} The composite neonatal complication rate and admittance to neonatal intensive care unit (NICU) was significantly lower in the FR group compared with the expectant management group

Table 1. Pregnancy and neonatal outcomes of higher order pregnancies who had expectant management, reduced to twins and reduced to singleton.

Pregnancy outcomes	No. (%) ^a				P value
	Composite (n=24)	(A) Expectant management (n=13)	(B) Reduction to twins (n=10)	(C) Reduction to singleton (n=1)	
Chorionicity (after reduction)					-
TC	16 (66.7)	8 (61.5)	-	-	-
DC	7 (29.2)	4 (30.7)	8 (80.0)	-	-
MC	1 (4.2)	1 (7.6)	2 (20.0)	1 (100)	-
Method of reduction					-
Intracardiac KCL injection		-	10 (100)	1 (100)	-
Radiofrequency ablation		-	-	-	-
Miscarriage of whole pregnancy (<24 weeks)		0	0	0	-
Miscarriage of 1 fetus in pregnancy (<24 weeks)		1 (7.6)	0	0	0.517
Pregnancies with at least 1 IUGR fetus		10 (76.9)	5 (50.0)	0	0.008
Maternal complications					
PIH/PE		2 (15.3)	3 (30.0)	0	0.316
GDM		5 (30.6)	2 (20.0)	0	0.087
PPROM		2 (15.3)	0	0	0.195
Gestational age at delivery, mean $\pm$ SD, weeks		34.2 $\pm$ 19(d)	36.3 $\pm$ 11.5	40	0.014
<30		2 (15.6)	0	0	0.195
30–34		4 (30.7)	2 (20.0)	0	0.289
>34		7 (53.8)	8 (80.0)	1 (100)	0.018
Neonatal outcomes		(n=37)	(n=20)	(n=1)	
Outcome at birth					
IUFD at 24 weeks		1 (2.7)	-	-	0.609
Live births		36 (97.3)	20 (100)	1 (100)	0.609
Mean birth weight, g		1884	2346	3340	<0.001
<1500		9 (24.3)	1 (5.0)	-	
1500–2000		9 (24.3)	1 (5.0)	-	
>2000		19 (51.3)	18 (90.0)	1 (100)	
NICU stay		15	8		0.321
Mean duration of NICU stay (days)		26 (70.2)	8 (40.0)		<0.001
Neonatal morbidity (composite) ^b		16 (43.2)	4 (20.0)	0	<0.001
RDS		9 (24.3)	0	0	<0.001
Intubation		12 (32.4)	6 (30.0)	0	0.371

Table 1. Pregnancy and neonatal outcomes of higher order pregnancies who had expectant management, reduced to twins and reduced to singleton. (Cont'd)

Pregnancy outcomes	No. (%) ^a				P value
	Composite (n=24)	(A) Expectant management (n=13)	(B) Reduction to twins (n=10)	(C) Reduction to singleton (n=1)	
Hypoglycaemia		4 (11.0)	0	0	0.037
Sepsis		0	0	0	NA
NEC		1 (2.7)	0	0	0.602
Birth asphyxia		1 (2.7)	0	0	0.602
HIE					

DC: dichorionic; GDM: gestational diabetes mellitus; HIE: hypoxic ischaemic encephalopathy; IUFD: intrauterine fetal demise; KCL: potassium chloride; MC: monochorionic; NA: not applicable; NEC: necrotising enterocolitis; NICU: neonatal intensive care unit; PIH/PE: pregnancy-induced hypertension/preeclampsia; PPROM: preterm premature rupture of membrane; RDS: respiratory distress syndrome; SD: standard deviation; TC: term childbirth

^a All values in no. (%) except gestational age at delivery, mean $\pm$ SD.

^b Excluded 1 case of IUFD after 24 weeks.

($P < 0.001$). Lower rates of respiratory distress syndrome, intubation and sepsis were also observed in the FR group ($P < 0.05$). However, rates for necrotising enterocolitis, birth asphyxia, hypoxic ischaemic encephalopathy and hypoglycaemia were similar across both groups.

The expectant management group was more likely to have at least 1 intrauterine growth restriction fetus ($P = 0.008$). There was no significant difference in rates of spontaneous fetal loss, intrauterine death, preterm premature rupture of the membranes and length of NICU stay. No neonatal and post-neonatal deaths were observed in our cohort.

There are some reported cases of anencephaly and limb amputation associated with FR.⁹ Spontaneous loss of whole pregnancy has been reported as 8.1% and 4.4% in reduced versus non-reduced triplets respectively.¹⁰ None of these complications were observed in our cohort. This may be because all procedures were carried out by specialists who are considered to be experts in the field and pregnancies were followed up very closely.

A limitation of this study is its retrospective nature and relatively small sample size, owing to the loss of follow-ups for many foreign patients seen at the hospital. Some incomplete data sets had to be excluded and as a result, we could not obtain statistical power to demonstrate some reductions in neonatal morbidities in babies born following MFPR.

The strength of our study lies in the fact that it is the first and largest study of FR in higher-order pregnancies in Southeast Asia with comprehensive perinatal outcomes. The expectant management

group made up almost one-third of all triplet births in Singapore during the study period. Our study provides valuable data, which will be useful in counselling women with higher-order pregnancies.

In conclusion, FR prolongs GA at delivery and reduces neonatal morbidity rates. For women who chose expectant management, close follow-up at a tertiary maternity unit that provides antenatal care to high-risk pregnancies and neonatal support can lead to superior neonatal outcomes.

REFERENCES

1. Registry of Births and Deaths, Immigration & Checkpoints Authority Singapore. Report on registration of births and deaths 2022.
2. Pharoah PO. Risk of cerebral palsy in multiple pregnancies. *Clin Perinatol* 2006;33:301-13.
3. Dodd JM, Dowswell T, Crowther CA. Reduction of the number of fetuses for women with a multiple pregnancy. *Cochrane Database Syst Rev* 2015;CD003932
4. Chaveeva P, Kosinski P, Puglia D, et al. Trichorionic and dichorionic triplet pregnancies at 10-14 weeks: outcome after embryo reduction compared to expectant management. *Fetal Diagn Ther* 2013;34:199-205.
5. Antsaklis A, Souka AP, Daskalakis G, et al. Embryo reduction versus expectant management in triplet pregnancies. *J Matern Fetal Neonatal Med* 2004;16:219-22.
6. Wimalasundera RC. Selective reduction and termination of multiple pregnancies. *Semin Fetal Neonatal Med* 2010;15:327-35.
7. Bastek JA, Sammel MD, Paré E, et al. Adverse neonatal outcomes: examining the risks between preterm, late preterm, and term infants. *Am J Obstet Gynecol* 2008;199:367.e1-8.
8. Watkins WJ, Kotecha SJ, Kotecha S. All-Cause Mortality of Low Birthweight Infants in Infancy, Childhood, and Adolescence: Population Study of England and Wales. *PLoS Med* 2016;13:e1002018.

9. Ibérico G, Navarro J, Blasco L, et al. Embryo reduction of multifetal pregnancies following assisted reproduction treatment: a modification of the transvaginal ultrasound-guided technique. *Hum Reprod* 2000;15:2228-33.
10. Papageorghiou AT, Avgidou K, Bakoulas V, et al. Risks of miscarriage and early preterm birth in trichorionic triplet pregnancies with embryo reduction versus expectant management: new data and systematic review. *Hum Reprod* 2006;21:1912-7.

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