

Triplet pregnancy with fetal reduction: experience in Hong Kong

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ABSTRACT

Introduction: Triplet and higher-order multiple pregnancies are well known to be associated with increased adverse outcomes. This study reviewed the perinatal outcomes in women with a triplet pregnancy who underwent fetal reduction versus expectant management at a university hospital in Hong Kong.

Methods: This was a retrospective review of triplet pregnancies at Prince of Wales Hospital in Hong Kong from 1 January 2008 to 30 September 2014. Women carrying a triplet pregnancy were classified as having had expectant management, fetal reduction to twins, or fetal reduction to a singleton. Maternal and pregnancy characteristics were compared. Outcome measures included fetal loss, gestational age at delivery, birth weight, neonatal survival rate, neonatal death, neonatal complications, and need for and length of neonatal intensive care unit stay.

Results: A total of 52 triplet pregnancies were identified. One pregnancy that was lost to follow-up and one that was terminated were excluded. The majority of pregnancies (84%) were the result of assisted reproductive technology. Fetal reduction was performed in 26 (52%) pregnancies, of which 22 were reduced to twins and four to a singleton. The mean gestations at delivery were 32.6, 35.2, and 39.6 weeks in the expectant management, fetal reduction

to twins, and fetal reduction to a singleton groups, respectively. Significantly more pregnancies with expectant management resulted in a preterm birth. All pregnancies with fetal reduction to a singleton resulted in a term birth. A higher mean birth weight, lower neonatal death rate, and reduced need for admission to and length of stay in the neonatal intensive care unit were observed in the fetal reduction groups.

Conclusions: Approximately 50% of women with a triplet pregnancy in Hong Kong elected to undergo fetal reduction. This was associated with a significant reduction in extreme preterm delivery and associated morbidity and mortality.

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▶ A video clip showing triplet pregnancy with fetal reduction skills is available at <www.hkmj.org>



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New knowledge added by this study

- This is the first study of fetal reduction in triplet pregnancy in Hong Kong.
- About half of women with a triplet pregnancy in Hong Kong would elect to undergo fetal reduction.
- Fetal reduction can significantly prolong the gestation at delivery and significantly reduce preterm delivery to <32 weeks.

Implications for clinical practice or policy

- Women with a triplet pregnancy should be adequately counselled on the benefits and risks of fetal reduction to allow them to make an informed decision.

Introduction

The recent increasing availability and popularity of assisted reproductive technology (ART) has resulted in an increase in the incidence of multiple pregnancies.¹ In the United States, the incidence of triplet pregnancies has increased two- to three-fold since the early 1980s.² In Hong Kong, there was a 2.3-fold increase in ART procedures from 2009 to 2015, reaching over 11 000 procedures per year.³ The Council on Human Reproductive Technology

of Hong Kong issued the Code of Practice on Reproductive Technology & Embryo Research in 2013 and limited the number of embryos transferred per cycle to three. Despite this recommendation, there has been no drop in the number of multiple pregnancies following ART, and the rate has remained at 6% since 2010.³ Thus multiple pregnancy is still a major obstetric concern in Hong Kong.

Triplet and higher-order multiple pregnancies are well known to be associated with increased

adverse outcomes including maternal medical complications, pregnancy loss, intrauterine growth restriction, and preterm delivery. Triplet pregnancies have a four-fold increased risk of birth of <29 weeks compared with twin pregnancies.⁴ This is of particular concern as it significantly increases the perinatal morbidity and mortality due to prematurity. The risk of infant death in triplets is 3 times higher than that in twins.⁴

Reduction of triplets or higher-order multiple pregnancies has been performed since the 1980s. A meta-analysis of the early prospective non-randomised studies suggested that reduction of triplet pregnancies was associated with a reduction in maternal and fetal adverse outcomes.⁵ More importantly, the rate of early premature delivery (<32 weeks) can significantly be reduced following fetal reduction (FR), from 26%-33% to 5.5% for FR to a singleton and 10%-17% for FR to twins.⁶⁻⁸ Nonetheless, it is associated with procedure-related pregnancy loss in 4.5%-9.6% of cases when performed by fetal intracardiac injection of potassium chloride (KCl), and 8.8%-15% for cord coagulation.⁸⁻¹¹

The objective of this study was to compare the perinatal outcomes for triplet pregnancy with and without FR at a university hospital in Hong Kong.

Methods

This was a retrospective cohort study conducted at Prince of Wales Hospital, Hong Kong. Triplet pregnancies with an expected date of confinement from 1 January 2008 to 30 September 2014 were retrieved from the prenatal diagnostic unit database and the Specialty Clinical Information System database. Demographics, and pregnancy and perinatal outcomes were reviewed. The data retrieval and review were performed by the first author, a medical officer from the department, who was not blinded to the study hypothesis. Women who carried a triplet pregnancy were classified into three groups: expectant management, FR to twins, or FR to a singleton.

Chorionicity and amnionicity were assessed during the first trimester by ultrasound. Women with a triplet pregnancy were offered counselling about the benefits and risks of expectant management versus FR to twins or a singleton. Specifically, women were counselled that approximately one third of triplet pregnancies resulted in preterm birth before 32 weeks of gestation. The aim of FR was primarily to reduce the risk of early preterm birth. Such risk can be reduced to 10%-18% following FR to twins and to 5%-8% if reduced to a singleton, although the procedure associated with a miscarriage rate of 5%-15%, depending on the method used.⁶⁻¹¹ Ultimately, the decision for FR to twins or a singleton was dictated first by the mother's wishes and second by whether FR was technically feasible.

三胞胎與減胎術：香港的經驗

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引言：眾所周知，三胞胎或以上多胎妊娠的懷孕風險會增加。本研究回顧香港一所大學醫院內三胞胎孕婦進行減胎術或預期式治療的圍產期結果。

方法：我們對2008年1月1日至2014年9月30日期間在香港威爾斯親王醫院的三胞胎產婦進行回顧分析，並把她們分為以下三類：預期式治療、減至雙胞胎和減至單胎，並比較產婦和懷孕胎兒的特徵。測量結果包括胎兒丟失率，分娩胎齡，新生兒的出生體重、存活率、死亡率和併發症，以及新生兒是否需要入住新生兒深切治療病房和其入住時間。

結果：研究期間共有52名孕婦懷有三胞胎，其中1例失訪，另1例終止懷孕，所以這兩例從研究中排除。大多數三胞胎懷孕（84%）均是由輔助生殖技術所得。有26例（52%）進行減胎術，其中22例減至雙胎，4例減至單胎。預期式治療、減至雙胎和減至單胎的平均分娩期依次為32.6週、35.2週和39.6週。預期式治療的早產個案明顯較多。所有減至單胎的個案均在足月分娩。接受減胎術的組別當中新生兒的平均出生體重較高、死亡率較低，新生兒入住深切治療病房的比率和時間較少。

結論：香港約有50%的三胞胎孕婦選擇接受減胎術。減胎術能明顯減低極早產率和連帶的罹病率及死亡率。

All procedures were performed in accordance with the Offences Against the Person Ordinance. The FR procedures carried out at the Prince of Wales Hospital were performed under real-time ultrasound guidance by Maternal and Fetal Medicine (MFM) specialists or supervised trainees. Some procedures were performed in the private sector. Choice of fetus(es) to be reduced depended on the presence of fetal abnormalities, placental location, and technical feasibility. Fetal gender was not revealed to the parents to avoid gender selection. Fetal intracardiac KCl injection was performed in fetuses with a separate placenta, that is, in trichorionic triamniotic (TCTA) triplets or when feticide was performed in both monochorionic fetuses of a dichorionic triamniotic (DCTA) pregnancy. A 20G needle was inserted transabdominally into the fetal heart and 1-5 mL of 14.9% KCl injected until fetal asystole was observed. Bipolar cord coagulation (BPC) or radiofrequency ablation (RFA) of the umbilical cord was performed in monochorionic fetuses in DCTA or monochorionic triamniotic (MCTA) triplets. In BPC, a 2-mm or 3-mm bipolar forceps was inserted transabdominally through a 3.9-mm trocar (Karl Storz, Tuttlingen, Germany) and the umbilical cord was grasped. Electrocautery was performed at a power setting of 20-60 W for a duration of 30-60 seconds. Two to three adjacent sites on the cord were cauterised. Cessation of blood flow through the

umbilical cord was confirmed by colour and/or pulsed wave Doppler. In RFA, the radiofrequency needle (LaVeen SuperSlim Needle Electrode radiofrequency probe, 17G, 15 cm long; Massachusetts, United States) was inserted percutaneously into the fetal abdomen at the site of cord insertion. The prongs of the device were deployed and radiofrequency energy was applied in a stepwise fashion starting from 30 W and progressing to a maximum of 100 W; each energy level lasted no more than 2 minutes. Energy was applied until no blood flow was observed in the umbilical cord by colour and pulsed wave Doppler and a terminal fetal bradycardia was detected.

Women were discharged within 24 hours of the procedure, and were followed up 1 week later to confirm viability of the remaining fetus(es). Women who carried triplets and elected expectant management underwent elective caesarean delivery at 34 weeks. Monochorionic twins were delivered at 37 weeks and dichorionic twins at 38 weeks. Earlier delivery was indicated if there were maternal or fetal complications. The pregnancy outcomes studied included any pregnancy loss, gestational age at delivery, birth weight, neonatal survival rate, neonatal death, and neonatal complications: respiratory distress syndrome, chronic lung disease, intraventricular haemorrhage, necrotising enterocolitis, retinopathy of prematurity, neonatal sepsis, need for neonatal intensive care unit (NICU) care, and median length of NICU stay.

Ethics approval was obtained from the Institutional Review Board (CREC Ref No: 2016.697) with informed consent waived. The SPSS (Windows version 21.0; IBM Corp, Armonk [NY], US) was used for statistical analysis. Fisher's exact test was used for categorical data, and Student's *t* test for comparing the means between the expectant management and FR groups. A *P* value of <0.05 was taken as statistically significant.

Results

There were 52 triplet pregnancies during the study period. Two cases were excluded from analysis as one was lost to follow-up after 13 weeks of gestation, and the other had a termination of pregnancy (TOP) at 8 weeks for social reasons. Of the included pregnancies, 84% (42/50) were the result of an ART procedure, of which 14 resulted from ovulation induction and 28 from in-vitro fertilisation. Among those conceived by ovulation induction, seven also included intrauterine insemination. In these 42 pregnancies conceived by ART, 33 (78.6%) were TCTA, eight (19.0%) were DCTA, and one (2.4%) was MCTA.

In the 50 cases included in the analysis, 26 (52.0%) pregnancies underwent FR and the remaining 24 (48.0%) had expectant management.

Of the 26 cases of FR, 22 (84.6%) were reduced from triplets to twins and four (15.4%) from triplets to a singleton. Two of the pregnant women in the expectant management group elected FR, however, this could not be done due to technical difficulties and so they were managed conservatively. All except three FR procedures were performed at the Prince of Wales Hospital between 10 and 13 weeks of gestation. The three cases of FR performed in the private sector had fetal intracardiac KCl injection between 7 and 9 weeks of gestation.

Maternal characteristics and pregnancy outcomes are shown in Table 1. Women who underwent FR were 1 to 2 years older than those who elected expectant management. Parity, method of conception, chorionicity, and method of feticide between the three groups were similar. There was no miscarriage of the whole pregnancy in any of the three groups although five pregnancies that were managed expectantly had spontaneous fetal loss of one of the fetuses, and one pregnancy with FR to twins miscarried one twin following FR. The numbers of spontaneous fetal losses before 24 weeks (ie miscarriage rate) were 6.9% (5/72) and 2.1% (1/48) in the expectant management group and FR group, respectively, and there was no statistical significance between the two groups. There were three cases of preterm rupture of membranes (ROM) following FR and in all three cases the parents elected TOP. One woman had fetal intracardiac KCl injection to reduce a TCTA triplet pregnancy to twins at 11 weeks, but ROM occurred at 15 weeks of gestation. In the other two cases where feticide was performed to reduce the triplets to a singleton, one was a case of MCTA triplets reduced to a singleton with BPC of two fetuses at 13 weeks, and the other was TCTA triplets reduced to a singleton by fetal intracardiac KCl injection in two fetuses at 11 weeks of gestation. For these two cases, ROM occurred at 1 day and 11 weeks after FR, respectively. There were only two cases of cord coagulation in this study. Apart from the case of BPC in MCTA triplets that resulted in ROM, the other case was also MCTA triplets with RFA performed at 12 weeks for FR to twin pregnancy. The procedure was uncomplicated and the twins were subsequently delivered at 35 weeks of gestation. The gestational age at delivery was significantly higher in the FR groups. The mean gestation at delivery was 32.6 weeks in the expectant management group versus 35.2 and 39.6 weeks in the FR to two fetuses and one fetus, respectively. The risk of extreme preterm delivery was also significantly lower in those with FR (*P*=0.001). In women with expectant management, 16.7% had extreme preterm delivery of <28 weeks, and 29.2% delivered before 32 weeks. In women with FR to two fetuses, there was no case of extreme preterm delivery of <28 weeks, and 23.8% delivered before 32 weeks. All pregnancies with FR to a singleton had term

TABLE 1. Maternal characteristics and pregnancy outcomes of triplet pregnancies

	Mean ± standard deviation or No. (%) of patients			P value	
	(a) Expectant management (n=24)	(b) Reduction to twins (n=22)	(c) Reduction to a singleton (n=4)	(a) vs (b)+(c)	(b) vs (c)
Maternal age (years) at expected date of confinement	32.7 ± 5.2	35.5 ± 2.6	33.5 ± 2.4	0.037	0.188
Conception				0.132	0.289
Spontaneous	6 (25.0)	1 (4.5)	1 (25.0)		
Assisted reproduction	18 (75.0)	21 (95.5)	3 (75.0)		
Nulliparous	21 (87.5)	18 (81.8)	4 (100.0)	1	1
Chorionicity				0.070	0.008
Trichorionic triamniotic	12 (50.0)	20 (90.9)	1 (25.0)		
Dichorionic triamniotic	8 (33.3)	1 (4.5)	2 (50.0)		
Monochorionic triamniotic	4 (16.7)	1 (4.5)	1 (25.0)		
Method of fetal reduction				N/A	0.289
Fetal intracardiac potassium chloride injection	N/A	21 (95.5)	3 (75.0)		
Bipolar cord coagulation	N/A	0	1 (25.0)		
Radiofrequency ablation of umbilical cord	N/A	1 (4.5)	0		
Miscarriage of the whole pregnancy (<24 weeks)	0	0	0	1	1
Miscarriage of one of the fetuses in the pregnancy (<24 weeks)	5 (20.8)	1 (4.5)	0	0.093	1
No. of pregnancies with mid-trimester TOP (<24 weeks)	0	1 (4.5)	2 (50.0)	0.236	0.052
Pregnancy with at least one IUGR fetus (excluding mid-trimester TOP cases)	2 (8.3)	1 (4.8)	0	1	1
Fetuses alive prior to delivery, including TOP and intrauterine death					
Pregnancies with no fetus alive	0	1	2	0.236	0.052
Pregnancies with 1 fetus alive	0	2	2	N/A	N/A
Pregnancies with 2 fetuses alive	6	19	N/A	N/A	N/A
Pregnancies with 3 fetuses alive	18	N/A	N/A	N/A	N/A
Gestation at delivery (weeks)	32.6 ± 4.0	35.2 ± 3.3	39.6 ± 0.6	0.009	0.080
Gestation at delivery (weeks)				0.001	0.704
24-27	4 (16.7)	0	0		
28-31	3 (12.5)	5 (23.8)	0		
32-35	14 (58.3)	4 (19.0)	0		
≥36	3 (12.5)	12 (57.1)	2 (100.0)		

Abbreviations: IUGR = intrauterine growth restriction; N/A = not applicable; TOP = termination of pregnancy

birth. None of the pregnancies was complicated by twin-to-twin transfusion syndrome and intrauterine growth restriction occurred in only two and one pregnancies in the expectant management and FR to twins groups, respectively.

The neonatal outcome of the fetuses who survived beyond 24 weeks are reported in Table 2. There were two intrauterine fetal deaths, one in the expectant management group and one in the FR to twins group. All seven neonatal and post-neonatal deaths occurred in the expectant management group. These infants were all delivered <25 weeks

and died of complications of prematurity. The mean birth weights in the FR groups to twins and a singleton were 553 g and 1073 g higher than that in the expectant management group, respectively. The need for NICU care (P=0.003) and length of NICU stay (P=0.040) were significantly higher in the expectant management group with no FR. Neonatal morbidities including respiratory distress syndrome, chronic lung disease, intraventricular haemorrhage, necrotising enterocolitis, retinopathy of prematurity, and neonatal sepsis were not statistically significant between the groups.

TABLE 2. Neonatal outcome in fetuses surviving beyond 24 weeks

	No. (%), mean \pm SD, or median (IQR)			P value	
	(a) Expectant management (n=67)	(b) Reduction to twins (n=41)	(c) Reduction to a singleton (n=2)	(a) vs (b) + (c)	(b) vs (c)
Fetal outcome at birth				1	1
Intrauterine fetal death after 24 weeks	1 (1.5)	1 (2.4)	0		
Live birth	66 (98.5)	40 (97.6)	2 (100.0)		
Birth weight (g)	1615 \pm 577	2168 \pm 524	2688 \pm 237	<0.001	0.143
Neonatal and post-neonatal outcome (% of live birth)				0.041	1
Alive (after 1 year)	59 (89.4)	40 (100.0)	2 (100.0)		
Neonatal and postnatal death	7 (10.6)	0	0		
Early neonatal death (\leq 7 days)	4 (6.1)	0	0		
Late neonatal death (8-28 days)	2 (3.0)	0	0		
Post-neonatal death (>28 days, within 1 year)	1 (1.5)*	0	0		
NICU care (% of live births)	39 (59.1)	12 (30.0)	0	0.003	1
Length of NICU stay (days)†	10 (0-21.5)	0 (0-22.3)	0	0.040	0.374
Neonatal morbidity (% of live birth)					
Respiratory distress syndrome	8 (12.1)	5 (12.5)	0	1	1
Chronic lung disease	4 (6.1)	3 (7.5)	0	1	1
Intraventricular haemorrhage	3 (4.5)	1 (2.5)	0	1	1
Necrotising enterocolitis	2 (3.0)	1 (2.5)	0	1	1
Retinopathy of prematurity	3 (4.5)	1 (2.5)	0	1	1
Sepsis	6 (9.1)	7 (17.5)	0	0.363	1

Abbreviations: IQR = interquartile range; NICU = neonatal intensive care unit; SD = standard deviation

* One neonatal death case occurred at 51 days

† Excluded intrauterine death, all neonatal and post-neonatal death

Discussion

Multiple pregnancy is an increasingly important problem in obstetric practice as a result of the success of fertility procedures. Their incidence is expected to continue to rise as fertility services both in Hong Kong and in other nearby countries such as Taiwan, Thailand, and Mainland China become more accessible and affordable. As shown in our cohort, over 80% of triplet pregnancies were conceived by ART. This is the first study of the outcomes of triplet pregnancies following FR in Hong Kong. Of note, FR may not be acceptable to all parents, and parental choice has a strong influence on decisions about intervention. To make the best informed choice, parents should be counselled adequately on the benefits and risks of expectant management versus FR. The provision of local data on perinatal outcomes following FR is an essential part of that counselling.

The primary aim of FR is to reduce neonatal morbidity consequent to prematurity. Our results show that FR in a triplet pregnancy has the benefit of increasing the gestation at delivery and reducing the risk of extreme preterm delivery earlier than 32

and 28 weeks. The mean gestation at delivery was 32.6 weeks in the expectant management group versus 35.2 and 39.6 weeks in the FR to two fetuses and one fetus, respectively. This indicates that the performance of FR in Hong Kong is comparable with that reported in the literature and our results reaffirm previously reported data in which FR in triplet pregnancies to twins can prolong the pregnancy by approximately 3 weeks.¹² In women with expectant management, 16.7% and 29.2% had extreme preterm delivery before 28 weeks and 32 weeks, respectively. In women with FR to two fetuses, there was no extreme preterm delivery of <28 weeks, and 23.8% delivered before 32 weeks. The risk of preterm delivery earlier than 32-33 weeks following FR has been reported to be between 24% and 37%,^{7,13-15} which are comparable to our results. All women with FR to one fetus had term deliveries. Despite the prolongation of pregnancy, however, the overall survival following FR was not significantly different to that following expectant management (Table 1). In fact, studies of FR in triplet pregnancies have not shown an increase in perinatal survival.^{12,13}

Prolongation of pregnancy in the FR group leads to improvement in a number of outcomes. The FR group had a significantly higher birth weight. The need for NICU care and length of NICU stay were significantly lower. The seven neonatal deaths in our cohort were all of neonates from the expectant management group who were delivered <25 weeks and died of complications of prematurity. We were, however, unable to show a difference in neonatal morbidity due to the small numbers in each group.

The rates of spontaneous loss of the whole pregnancy in reduced versus non-reduced triplets have previously been reported to be 8.1% and 4.4%, respectively,⁷ although such loss rate can be reduced with increasing experience so that it is comparable with that in non-reduced triplets.^{6,10,11} In our study, there was no spontaneous total pregnancy loss. This may be because all procedures were carried out by MFM specialists or trainees with expertise in invasive fetal procedures. There were fetal losses in both the expectant management and FR groups, but it was not statistically significant. Three cases had prelabour ROM after FR, and these parents elected TOP due to poor prognosis. Most studies of FR report a procedure-related pregnancy loss or miscarriage rate,^{6-8,10,11} but there are no data for the rate of prelabour ROM after FR in triplet pregnancies. In complicated monochorionic pregnancies, the rate of prelabour ROM following cord coagulation has been reported to be 20% to 30%.^{9,16,17} On the contrary, the prelabour ROM rate was 12% after fetal intracardiac KCl injection in multichorionic pregnancies.¹⁸

This study found that only maternal age influenced a decision to undergo FR but this is contrary to the findings of other studies.^{7,13,19} A possible explanation is that in women with advanced age, multiple pregnancy will add additional maternal risks during the pregnancy and may influence a decision to undergo FR. When choosing FR to twins or a singleton, our results showed that the chorionicity of the triplet pregnancies most likely affected their choice: 64% (21/33) of those with TCTA triplets chose to have FR although 95% (20/21) opted for reduction to twins. In DCTA and MCTA triplets, only 27% and 33% proceeded to FR, respectively. As our study only had two cases of RFA or BPC performed in MCTA triplets, we cannot conclude any reason for a low rate of FR by cord coagulation. It is, however, possible that women believed there was a higher risk of miscarriage associated with RFA or BPC.

It must be emphasised that in women who choose to reduce one fetus in a DCTA pregnancy, the best option is to reduce one fetus in the monochorionic pair, not the fetus with a separate placenta, by fetal intracardiac KCl injection. Although the latter is technically easier, there would be continued risks of twin-to-twin transfusion

syndrome or twin anaemia polycythaemia sequence when the singleton fetus is reduced to keep the monochorionic twins, and this poses significant risks to the pregnancy. The miscarriage risk before 24 weeks following FR of the fetus with a separate placenta has been reported to be as high as 23.5%.⁸ Therefore, women who elect to have FR of DCTA triplets to twins should be referred to a tertiary unit with expertise in FR and where more advanced techniques are readily available. Nevertheless, the best perinatal outcome in any type of triplets will be achieved by reducing two fetuses resulting in a singleton pregnancy.⁸ Women along with their partner should be aware of this and be adequately counselled so that they may make an informed decision.

This is the first study of FR in triplet pregnancy in Hong Kong. It provides valuable data on the local experience in FR that is useful in parental counselling. The strength of this study is that comprehensive perinatal outcomes were obtained in all pregnancies except two.

This study has limitations. First, the number of cases included was small, although we believe this is the largest cohort possible to be reported in Hong Kong as our hospital has the highest number of deliveries and receives referrals for FR from private obstetricians and other obstetric units in Hong Kong. Second, the number of cord coagulation procedures was limited, and no further analysis was possible to determine which cord coagulation procedure is superior.

Conclusions

Approximately 50% of women with a triplet pregnancy in Hong Kong elected to undergo FR, which can significantly prolong the gestation at delivery and significantly reduce preterm delivery of <32 weeks, although it is associated with risk of miscarriage and complications such as ROM. Women carrying a triplet pregnancy should be adequately counselled about the benefits and risks of FR so that they can make an informed decision.

Declaration

All authors have disclosed no conflicts of interest.

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