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Original Article

Clinical outcomes of multifetal pregnancy reduction in trichorionic and dichorionic triplet pregnancies: A retrospective observational study

Yaqiong Liu^{b, c}, Yan Shen^a, Hong Zhang^a, Yi Tang^a, Guangxiu Lu^{a, c}, Ge Lin^{a, b, c}, Fei Gong^{a, b, c, *}^a Reproductive and Genetic Hospital of CITIC-Xiangya, Changsha, China^b Institute of Reproductive and Stem Cell Engineering, School of Basic Medicine, Central South University, China^c Key Laboratory of Reproductive and Stem Cell Engineering, Ministry of Health, China

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ABSTRACT

Objective: To observe the pregnancy and perinatal outcomes of trichorionic triplet (TCT) and dichorionic triplet (DCT) pregnancies with or without multifetal pregnancy reduction (MFPR).**Materials and methods:** This was a retrospective study of 732 TCT and 118 DCT pregnancies after IVF/ICSI cycles between October 1999 and May 2014 at the Reproductive & Genetic Hospital of CITIC-Xiangya. The TCT and DCT groups were subdivided into three subgroups: MFPR to single fetus group, MFPR to twins group and expectant group. Pregnancy and perinatal outcomes were compared between different subgroups.**Results:** The resulting subgroups were TCT-Expectant (n = 40), TCT to twin (n = 610), TCT to single (n = 22), DCT-Expectant (n = 17), DCT to twin (n = 50), and DCT to single (n = 22). The groups with MFPR had the better pregnancy and perinatal outcomes. Meanwhile, the significantly higher abortion rates but lower live birth and take home baby rates were found in TCT-Expectant group and DCT-Expectant group (all $P < 0.05$). Besides, the abortion rate of DCT-Expectant group was much higher than TCT-Expectant group (41% verse 15%, $P = 0.032$). As for the perinatal outcomes, retaining single fetus group showed the advantage of higher birth weight, and elder gestational age in both DCT and TCT pregnancies (all $P < 0.05$).**Conclusion:** For DCT and TCT pregnancies, MFPR application could reduce the miscarriage rate, while improving live birth and take home baby rates compared to the expectant groups. Especially, when reduced to a single fetus, MFPR could provide the better perinatal outcomes.© 2018 Taiwan Association of Obstetrics & Gynecology. Publishing services by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

The incidence of multiple pregnancies has increased substantially in recent decades with the development of the assisted reproduction techniques (ART) [1]. This is because the initial step in ART always involving controlled ovarian hyperstimulation, resulting in the availability of multiple embryos [2]. Besides, multiple embryos transferring in ART treatment cycles are applied to maximize pregnancy rate [3–5]. Meanwhile, the complications and

risks for both women and infants in multifetal pregnancies are well recognized, including the increased rates of abortion, preterm birth, cesarean section, and postpartum hemorrhage [6]. In addition, neonatal morbidity and mortality rates may also increase due to malformation and intrauterine growth retardation in multifetal pregnancy [7]. Especially, the multiple pregnancies containing a monochorionic (MC) component, with fetuses that share a placenta, are related with unique complications, such as twin-to-twin transfusion syndrome (TTTS) and severe birth weight discordance, because of the vascular anastomoses in the single placental bed, with subsequently increased morbidity and mortality for the embryos and neonates [8]. To reduce the risks of multiple pregnancies, the option of multifetal pregnancy reduction (MFPR) has

* Corresponding author. Institute of Reproductive & Stem Cell Engineering, Central South University, Changsha, Hunan Province 410078, China. Fax: +86 731 84497661.

E-mail addresses: linggf@hotmail.com, gfdirector@126.com (F. Gong).

applied with the intention of increasing the likelihood of a good outcome for the pregnancy [9].

As for MFRP, there is no consensus of the optimal strategy so far. Some researchers believe that retaining a single embryo after early MFPR can result in the best pregnancy outcomes [10–12]. However, some studies showed that MFPR would also increase the possibility of miscarriage. Chaveeva et al. [13] found that the miscarriage rate was higher in ER (embryo reduction) to 1 fetus group compared with ER to 2 fetus group, while the miscarriage rate was lowest in expectantly managed triplet pregnancies. In addition, they believed that the recent advances in neonatal intensive care and obstetric care could improve the outcome for earlier term and lower-weight births, which could support multiple pregnancies expectantly management [13]. In addition, there are very few literature about the management of dichorionic triplet (DCT) pregnancies, where two of the three fetuses share a placenta. Among these studies, the obstetrical outcome was favorable when the monochorionic twin component was reduced, with an extension of gestation of 52 days [14,15]. So far, the optimal approach for MFPR remains unknown and studies about early MFPR of DCT pregnancies are relatively rare, especially for those reduced to monochorionic (MC) twins.

The aim of this study was to observe the pregnancy and perinatal outcomes of different MFPR strategies (to retain singleton or twin pregnancies) in DCT and TCT pregnancies. Herein, we conducted a retrospective study on triplet pregnancies from October 1999 to May 2014 after IVF/ICSI cycles at the Reproductive & Genetic Hospital of CITIC Xiangya and the pregnancy and perinatal outcomes were compared between different subgroups.

Materials and methods

Patients

A retrospective analysis of 732 trichorionic triplet (TCT) and 118 DCT pregnancies after IVF/ICSI cycles was conducted. The women were enrolled and grouped according to DCT or TCT pregnancies and sub-grouped according to whether they underwent MFPR and the number of retained embryos. The study was approved by the ethics committee of the hospital and written informed consent was waived as the retrospective nature of this study.

Spontaneous fetal reduction (SPR) and MFPR

All triple pregnancies resulting from ART treatment were rechecked whether SPR had happened. SPR was diagnosed according if B-ultrasound showed empty gestational sac or one or more embryos disappeared after identifying heart tube beat. This time point after ET of discovery of SPR was record, and the last ultrasound check was performed 45 days after embryo transfer (ET) in our IVF unit.

Patients without SPR were counseled about MFPR in our hospital. The probable complications of multiple fetal pregnancies and the risks or benefit of MFPR were explained. The doctors gave advice about the embryo(s) which should be reduced according to their condition and position. Final decisions about the whether to undergo MFPR and the number of retained embryos were made by the patients, depending on their religious beliefs and personal preference.

All of the MFPRs were performed during Day 45 to Day 65 after ET. A trans-abdominal approach with a 20-G spinal needle (15 cm in length) under ultrasound guidance was used. Potassium chloride (10% Potassium chloride solution, 2 mL) was injected into the fetal thorax. No maternal sedation or local anesthesia was given. Antibiotics and luteal support were given after the MFPR referring to

patients' condition. Three days after MFPR, B ultrasound was undertaken to confirm that the reduced fetus was dead.

Definitions

DCT were diagnosed by trans-vaginal ultrasound based on the number of placental disks, the presence of the "lambda sign" or the "T sign" [16], and the number of amniotic cavities and yolk sacs in every gestational sac. Abortion was defined according to the Chinese Ministry of Health [17] as: pregnancies stopped before the 28th gestational week or the aborted fetus was less than 1000 g. Perinatal mortality referred to stillbirths (more than 28 gestational weeks or 1000 g birth weight) and deaths in the first week of life. Take home baby was getting at least one live baby, and the live baby was at least 28 gestational weeks, and lived for at least 1 month. Premature birth was delivery before 37 gestational weeks. Low birth weight was defined as birth weight less than 2500 g, and birth weight discordance was calculated using the formula: $([\text{birth-weight larger twin}] - [\text{birth-weight smaller twin}]) / [\text{birth-weight larger twin} \times 100\%]$ [18]. Congenital defects were classified as major malformations when they caused functional impairment or required surgical correction.

Statistical analysis

Statistical analysis was performed using the SPSS 22.0 software package (SPSS Inc., Chicago, IL). Values were expressed as mean \pm standard deviation (SD) since data were normally distributed. Differences between parameters among the groups were evaluated using t test. Differences between proportions were evaluated using the χ^2 or Fisher exact test. The forward conditional logistic regression analysis was used for detecting factors associated with taking a baby home. A *P* value of <0.05 was considered statistically significant.

Results

During this study period, SPR in the first 45 days after embryo transfer happened in 89 patients, and the total SPR rate was 10.47% (89/850). In addition, the SPR rate of DCT pregnancies was significantly higher than TCT pregnancies (24.57% (29/118) and 8.19% (60/732), respectively), although the average time after ET for discovery of SPR and the number of retaining fetus after SPR was similar in both DCT pregnancies and TCT pregnancies (Table 1).

There were 761 patients who did not undergo SPR, and they were subdivided refer to pregnancies type and the different MFPR strategies. The number of women in each of the subgroups were: DCT-Expectant ($n = 17$, DCT pregnancies without MFPR), DCT to single ($n = 22$, DCT pregnancies with MFPR to single embryo), DCT to MC twin ($n = 50$, DCT pregnancies with MFPR to MC twins), TCT-Expectant ($n = 40$, TCT pregnancies without MFPR), TCT to single (22 TCT pregnancies with MFPR to single embryo) and TCT to twin (610 TCT pregnancies with MFPR to twins). The demographic and clinical characteristics of the patients are presented in Table 2. Maternal age, BMI and duration of infertility were comparable between each subgroup in both TCT and DCT pregnancies (all $P > 0.05$).

Table 3 shows the comparison of pregnancy and perinatal outcomes among the TCT group. The TCT to twin group showed lower abortion rate, higher live birth and higher take-home-baby rates than the TCT-Expectant group. Besides, the perinatal outcomes were better in the TCT to single group compared to the TCT to twin group and the TCT Expectant group, with the longest gestational age at birth and highest birth weight, while the preterm rate and low birth weight rate were the lowest. Comparatively, the

Table 1
Spontaneous pregnancy reduction in triple pregnancies.

	DCT pregnancies (N = 118)	TCT pregnancies (N = 732)	P value
SPR rate	25% (29/118)	8% (60/732)	0.000
Time for discovery of SPR(days)	41.9 ± 1.3	38.4 ± 1.2	0.055
Number of retained fetus			
twin fetuses	62% (18/29)	77% (46/60)	0.151
single fetus	38% (11/29)	23% (14/60)	

Table 2
Demographic and clinical characteristics.

	TCT pregnancies			DCT pregnancies		
	Expectant (n = 40)	TCT to twin (n = 610)	TCT to single (n = 22)	Expectant (n = 17)	DCT to MC twin (n = 50)	DCT to single (n = 22)
Maternal age (years)	30.9 ± 4.35	31.37 ± 4.15	32.18 ± 4.07	31.0 ± 4.43	29.64 ± 4.19	29.73 ± 3.69
BMI (Kg/m ²)	21.58 ± 1.43	21.89 ± 2.8	21.07 ± 2.01	22.35 ± 2.55	22.13 ± 2.8	22.27 ± 3.05
Duration of infertility (years)	6.41 ± 3.79	5.62 ± 3.36	5.94 ± 3.43	6.88 ± 5.4	4.63 ± 2.65	5.05 ± 3.82
FET (N)						
used	5	170	5	4	13	4
not-used	35	440	17	13	37	18
ICSI (N)						
used	10	194	6	4	8	6
not-used	30	416	15	13	42	12

No statistically significant differences were found between the three groups in TCT and DCT pregnancies.

Table 3
Comparison of pregnancy and perinatal outcomes in TCT pregnancies.

	TCT pregnancies			P
	Expectant (n = 40)	TCT to twin (n = 610)	TCT to single (n = 22)	
Abortion rate (%)	15% (6/40)	5% (30/610) ^a	5% (1/22)	0.071
Live birth rate (%)	85% (34/40)	95% (577/610) ^a	95% (21/22)	0.099
Cesarean section rate (%) ^c	88% (30/34)	93% (539/577)	90% (19/21)	0.512
Preterm delivery rate (%) ^c	85% (29/34)	53% (304/577) ^a	14% (3/21) ^{a,b}	<0.001
Gestation at delivery (weeks) ^c	34.63 ± 2.279	36.17 ± 2.33 ^a	38.24 ± 2.02 ^{a,b}	<0.001
Number of fetus	96	1131	21	
Perinatal mortality rate (%)	1% (1/96)	1% (15/1131)	0% (0/21)	0.739
Number of alive fetus	95	1116	21	
Average birth weight (g) ^c	2083.5 ± 600.4	2432.8 ± 493.5 ^a	3128.6 ± 518.3 ^{a,b}	<0.001
Low birth weight rate (%) ^c	78% (74/95)	39% (434/1116) ^a	5% (1/21) ^{a,b}	<0.001
Birth weight discordance >25% (%) ^c	30% (10/33)	9.57% (53/554) ^a	—	—
Multiple fetuses alive (%) ^c	97% (33/34)	96% (554/577)	—	
one survivor	1	23	21	
two survivors	4	554	—	
three survivors	29	—	—	
Congenital malformation rate (%) ^c	1% (1/95)	2% (21/1116)	0% (0/21)	0.561
Take baby home rate (%)	85% (34/40)	94% (575/610) ^a	95% (21/22)	0.119

P: comparison between all three groups.

Bold value signifies P < 0.05.

^a Significant difference compared with expectant group.

^b Significant difference compared with TCT to twin group.

^c Perinatal outcomes are based on live birth.

gestational age and birth weight were lowest while the preterm rate and low birth weight rate was highest in the TCT Expectant group. Birth weight discordance >25% was higher in the TCT Expectant group than in the TCT to twin group.

As for DCT pregnancies, the abortion rate was significantly higher and the live birth and take home baby rates were significantly lower in DCT-Expectant group than in the DCT to single group. The caesarean section rate was higher in the MC twin group than the single group. The perinatal outcomes were similar in DCT and TCT pregnancies, that retaining single fetus group has the longest gestation and highest birth weight. Oppositely, the preterm rate and low birth weight rate was highest in DCT-Expectant group. The perinatal mortality rate from retaining MC twins was subtly higher than the other subgroups, although no statistical significance was found (Table 4).

Multivariate analysis for factors related to taking home a baby of Expectant groups (TCT-Expectant and DCT Expectant group) is shown in Table 5. This showed that duration of infertility was the only factor significantly associated with taking home a baby.

Discussion

Multiple pregnancies, were once considered an abnormal pregnancy, but recently they have become more common as the result of ART treatment. Unfortunately, they may lead to severe pregnancy complications. It can be a difficult decision whether they should opt for MFPR to improve pregnancy outcomes while taking the risk of miscarriage. In addition, it is unclear whether the choice to opt for MFPR is more important in DCT pregnancies. The aim of this study was to observe the differences in outcomes in DCT and

Table 4
Comparison of pregnancy and perinatal outcomes in DCT pregnancies.

	DCT pregnancies			P
	Expectant (n = 17)	DCT to MC twin (n = 50)	DCT to single (n = 22)	
Abortion rate (%)	41% (7/17)	14% (7/50) ^a	9% (2/22) ^a	0.019
Live birth rate (%)	59% (10/17)	82% (41/50)	91% (20/22) ^a	0.039
Cesarean section rate (%) ^c	70% (7/10)	95% (39/41)	70% (14/20) ^b	0.015
Preterm delivery rate (%) ^c	90% (9/10)	51% (21/41) ^a	10% (2/20) ^{a,b}	<0.001
Gestation at delivery (weeks) ^c	34.05 ± 2.53	36.12 ± 2.47 ^a	38.33 ± 2.33 ^{a,b}	<0.001
Number of birth	22	83	20	
Perinatal mortality rate (%)	0% (0/22)	10% (8/83)	0 (0/20)	0.1150
Number of alive birth	22	75	20	
Average birth weight (g) ^c	1840.5 ± 506.5	2389.1 ± 479.9 ^a	3052.5 ± 636.7 ^{a,b}	<0.001
Low birth weight rate (%) ^c	95% (21/22)	59% (44/75) ^a	15% (3/20) ^{a,b}	<0.001
Birth weight discordance >25% (%) ^c	30% (3/10)	11% (4/35)	—	
multiple fetuses alive (%) ^c	60% (6/10)	85% (35/41) ^a	—	
one survivor	4	5	20	
two survivors	—	35	—	
three survivors	6	—	—	
Congenital malformation rate (%) ^c	0% (0/22)	1% (1/75)	0% (0/20)	0.754
Take baby home rate (%)	59% (10/17)	80% (40/50)	91% (20/22) ^a	0.049

P: comparison between all three groups.

Bold value signifies P < 0.05.

^a Significant difference compared with expectant group.^b significant difference compared with TCT to twin group.^c perinatal outcomes are based on live birth; two stillbirths occurred in “DCT to MC twin” group, resulting the live birth number was 41.**Table 5**
Multivariate analysis for factors associated with taking a baby home as the pregnancy outcome in Expectant groups.

	Took a baby home (n = 44)	Did not take a baby home (n = 13)	Univariate P	OR ^a	95%CI ^a	Multivariate P ^a
age	30.2 ± 3.7	33.4 ± 5.5	0.018			0.463
Duration of infertility	5.8 ± 3.4	9.2 ± 6.0	0.011	1.198	1.029–1.395	0.020
primary infertility	23	6	0.698			0.971
Blastocyst transplant	5	1	0.705			0.530
Frozen embryo transplantation	6	3	0.412			0.492
ICSI used	10	4	0.554			0.523
Number of Embryo transferred	2.6 ± 0.6	2.5 ± 0.5	0.604			0.270
Number of oocyte pick-up	10.5 ± 6.0	9.8 ± 7.0	0.721			0.737

^a Forward conditional logistic regression analysis.

TCT pregnancies when women opted for MFPR to single or twin fetuses or decided not to undergo MFPR. The Results show that in both DCT and TCT pregnancies outcomes were improved if the women opted for MFPR. The differences were significant between the subgroups that opted for retaining a single fetus compared to those that opted not to have MFPR in both DCT and TCT pregnancies as for abortion, live birth, and take home baby rates.

The wide discussion about whether to perform MFPR or not and what is the best number of fetus to retain is aroused because that although MFPR may reduce the rate of premature birth, it may correspondingly increase the risk of miscarriage [13]. Studies showed that compared with expectant treatment, the miscarriage rate was higher and almost twice times in triple pregnancy ER groups [13,15]. Besides, the rate of pregnancy loss after MFPR was 9.1% and 5.1% in retaining single and twins in 24 weeks gestation, respectively [12]. The possible mechanisms leading to miscarriage following MFPR were considered as: firstly, procedure-related trauma or infection, in which case the miscarriage would be expected within 2 weeks of MFPR; secondly, the consequence of the resorbing dead fetoplacental tissue which may cause uterine contractions due to inflammatory response to dead fetoplacental tissue, which could result in miscarriage several weeks or months after MFPR [13,19,20]. However, in contrast with the previous studies, we found that the abortion rate in MFPR groups was lower than in the expectant groups in both TCT and DCT pregnancies. In addition, as for the TCT pregnancy group, the abortion rate was similar between retaining single group and retaining twin group. In addition, the abortion rate after

MFPR in this study was lower than that reported before. This observation suggested that using trans-abdominal intra-cardiac injection of potassium chloride solution under ultrasound guidance for embryo reduction technique between 45 days and 65 days after ET, is an effective and safe method of embryo reduction. With the improvement of ER technique, ER and the number of reduced embryo did not contribute to additional miscarriage.

SPR may occur before MFPR is undertaken, which may happen in about 25% of multiple pregnancies [21], but the mechanism of SPR is not clear. Some believe that SPR is associated with small uterine space and the relative lack of blood supply of the gestational sac caused by multiple pregnancies [21]; Besides, SPR is also related with the age of woman or with different controlled ovarian stimulation and ART methods. For example, Yi-Le Zhang [22] found that SPR rate is related to patients' age and the initial number of gestational sacs. SPR can improve pregnancy outcomes, but the later SPR occurs, the worse neonatal outcomes are. In their study, 78.4% SPR occurred before 8 gestational weeks [22]. In our study, the SPR rate was 10.47% in the first 45 days after ET, and the time for discovery of SPR was about 40 days after ET. Interestingly, we found that the SPR rate of DCT pregnancies was higher than that of TCT pregnancies. We assume that the SPR is related with the types of chorionicity, and monochorionic twins may lead to a higher chance of SPR. Thus, as for the triple pregnancies obtained from ART, we suggest to expect SPR in the first 45 days after ET.

Because of the unique features of a DCT pregnancy in terms of the placental structure, we should be cautious in dealing with

them. The abortion rate in the DCT- Expectant group was the highest in this study at 41% compared to 15% in the TCT group, thus we would not recommend expectant management in DCT pregnancies. The outcome of twin fetuses after DCT is pertinent in China due to the Chinese reproductive policies before 2016, which causing many infertile patients want to have two babies through one pregnancy. Thus, Chinese doctors need to pay attention to DCT pregnancies who want to retain twins after MFPR. Selective feticide by injecting one monozygotic twin fetus has not been considered to be feasible in MC twins, because of the risks of agonal inter-twin transfusion due to vascular anastomoses of 96% of vessels in the single placental bed [23,24]. A study that performed MFPR in 9 cases of DCT pregnancies to reduce one fetus of the MC pair at 6–8 gestational weeks using transvaginal ultrasound-guided puncture and aspiration of one monochorionic twin reached a late miscarriage rate of 33.3% [25]. Morlando et al. [26] performed a systematic review to analyze different treatments in DCT pregnancies. In 225 conservative management pregnancies, the miscarriage rate was 5.8%–13.3%, while the live birth rate was 90.7%; in 55 with reduction of the MC pair, the miscarriage rate was 7.6%–26.2%, and the birth rate was 83.6%; in 17 pregnancies retaining MC twins, the miscarriage rate was 9.65–47.3%. Thus, they recommended that expectant management is a reasonable choice when the top priority is a live born infant. But if the priority is to minimize severe preterm delivery, the most advisable option is fetal reduction. In this study, we found that the pregnancy and perinatal outcomes in the DCT groups with MFPR were better than in the expectant group. Therefore, we believe that MFPR is necessary in DCT pregnancies without SPR.

To the best of our knowledge, this study represents the largest number of cases of retaining MC twins after MFPR. When compared with those retaining a single fetus, the pregnancy and perinatal outcomes are relatively worse but without statistical difference. Therefore, we think the relatively higher miscarriage and perinatal mortality rate of MC twins were possibly associated with the abnormal and risky placental structure of the MC pair which may contribute to severe complications similar to TTTS, severe birth weight discordance, twin reversed arterial perfusion sequence (TRAP), twin anemia-polycythemia sequence (TAPS), and umbilical cord compression and entanglement [23], instead of the actual performance of embryo reduction. Compared with reduction of one fetus of the MC pair, the reduction of the fetus with a separate placenta may be an acceptable MFPR strategy with relatively lower miscarriage rate, despite the potential risks to MC twins. Apart from the common early MFPR, some centers carry out the vascular-occlusive technique, such as bipolar cord occlusion (BCO), radiofrequency ablation (RFA), fetoscopic laser occlusion of chorioangiopagous, and umbilical cord ligation. These vascular-occlusive techniques can selectively terminate an abnormal fetus, but those cases that need a selective reduction should be referred to a specialist center as soon as an indication is discovered; since the complexity and risk of the procedure increases with gestation [27]. The safety and prognosis of the vascular-occlusive technique needs further investigation, because the number of centers that can perform these operations is relatively small. To sum up, for DCT pregnancies, retaining a single fetus should be recommended to acquire the best outcomes. If patients have a strong desire to retain MC twins, it is important for them to attend regular antenatal care and receive timely obstetric intervention to avoid perinatal mortality.

For TCT pregnancies, the live birth rate and take-baby-home rate were similar in retaining single fetus and two fetuses, but a significant difference was seen between the TCT Expectant group and the TCT to single group. Nevertheless, in terms of the gestational age at delivery and birth weight, our results are consistent with the

previous studies [13,15], that retained singletons had longer gestation, lower preterm delivery, larger birth weight and lower low birth weight rates. The birth weight discordance >25% rate was higher in the TCT-Expectant (30.3%) than retaining two fetuses (9.57%), while the multiple-fetus live birth rate was quite close to that in the expectant group. We think that the birth weight discordance was mainly caused by intrauterine growth restriction.

Multivariate analysis for independent factors associated with taking home a baby in expectantly management groups showed that duration of infertility was a significant factor, which suggests that patients with a long duration of infertility were at risk of a poor pregnancy outcome if choose expectant treatment since they were less likely to take home a baby. We assume that the possible reason is that women with longer duration of infertility may suffer more complex physical and psychological problems which may exert adverse impact on maintain triplet pregnancies. Therefore, women with a long duration of infertility would not be advised to take the expectant strategy, but rather should be advised to opt for MFPR.

However, as a single center study, the number of patients was limited. Thus, some results with no significant difference might due to the small sample size in some sub-groups. A larger multiple center study would add more weight to the results. As a retrospective study the women were not randomly selected to receive the different treatments, therefore, there may be some bias in the results. However, the different reasons and desire that women may select MFPR or not, making randomization difficult to achieve.

Conclusion

In conclusion, for DCT and TCT multiple fetal pregnancies, MFPR could improve outcomes, and retaining a single fetus showed longer gestation periods and larger birth weights. For DCT pregnancies, retaining a single fetus is suggested for the best pregnancy and perinatal outcomes. But for keeping twins, the reduction of the fetus with a separate placenta could also produce acceptable outcomes.

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