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Trichorionic and Dichorionic Triplet Pregnancies at 10–14 Weeks: Outcome after Embryo Reduction Compared to Expectant Management

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Key Words

 $\label{eq:total-continuous} Triplet\ pregnancy \cdot Embryo\ reduction \cdot First\ trimester \cdot \\ Miscarriage \cdot Preterm\ birth$

Abstract

Objective: To compare the outcome of trichorionic triplet (TCT) and dichorionic triplet (DCT) pregnancies managed expectantly and those with embryo reduction (ER) at 10-14 weeks to twins or singletons. *Methods:* This was a retrospective study of triplet pregnancies with 3 live fetuses managed expectantly or by ER. Data were combined with the results of previous studies that used similar entry criteria and outcome measures. The management options were compared for rates of miscarriage and preterm birth <33 weeks. Results: In TCTs managed expectantly (n = 358), the rates of miscarriage and preterm birth were 3.1 and 35.1%. Compared to the expectantly managed TCTs, the rate of miscarriage was higher and preterm birth lower in TCTs with ER to 2 fetuses (n = 833, 7.3 and 13.1%, respectively) and TCTs with ER to 1 fetus (n = 78, 11.5 and 8.7%). In DCTs managed expectantly (n = 136), the rates of miscarriage and preterm birth were 8.8 and 46.0%. In DCTs with ER to 2 fetuses (n = 15) or ER to 1 fetus (n = 42), there was a non-significant increase in miscarriage (13.3 and 16.7%, respectively) and decrease in preterm birth (23.1 and 8%, respectively). **Conclusions:** In TCT and DCT pregnancies, ER increases the rate of miscarriage but reduces the rate of preterm birth.

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Introduction

Triplet pregnancies, compared to singletons and twins, are associated with a high risk of miscarriage before 24 weeks' gestation and early preterm birth. In a previous study of trichorionic triplet (TCT) pregnancies with 3 live fetuses at 10–14 weeks' gestation, including 185 that were managed expectantly and 180 that had embryo reduction (ER) to twins, we found that ER was associated with an increase in the rate of miscarriage but a decrease in early preterm birth [1–3].

In this study we examine the rates of miscarriage and early preterm birth in an extended series of 695 triplet pregnancies managed in our centre and 765 from 5 previous studies that used similar entry criteria and outcome measures. We compare the outcome of TCT and dichorionic triplet (DCT) pregnancies managed expectantly with those with ER to twins or singletons.

Table 1. Data on maternal age, method of conception, gestation at recruitment or embryo reduction, and pregnancy outcome in triplet pregnancies

	TCTs ^b			DCTs ^b		
	expectant (n = 229)	ER to 2 (n = 265)	ER to 1 (n = 34)	expectant (n = 123)	ER to 2 (n = 15)	ER to 1 (n = 29)
Maternal age, years Conception	34.2 (22.3 – 46.5)	34.7 (18.1 – 55.9)	34.3 (26.0 – 59.5)	34.3 (21.7 - 46.8)	36.5 (33.9-42.6) ^g	35.3 (23.2-46.0)
Spontaneous	30 (13.1)	31 (11.7)	6 (17.6)	23 (18.7)	0 (0.0)	0 (0.0) ^h
Ovulation induction	36 (15.7)	58 (21.9)	11 (32.4)	7 (5.7) ^f	0 (0.0)	0 (0.0)
In vitro fertilization	163 (71.2)	176 (66.4)	17 (50.0) ^d	93 (75.6)	15 (100.0)	29 (100.0) ^h
Recruitment gestation, weeks	12.1 (10.0 – 14.0)	11.9 (10.0-14.0) ^c	11.6 (10.0 – 14.0)	12.3 (9.3-14.0) ^f	12.0 (10.0-14.0)g	12.1 (10.0-14.0)
Delivery gestation ^a , weeks	34.0 (24.0 – 39.1)	36.0 (24.0-41.9) ^c	38.0 (24.1 – 40.0) ^{d, e}	$33.0(25.0-38.5)^{f}$	634.0 (24.4-37.2)	39.1 (30.0-41.7) ^h
Delivery <24 weeks	9 (3.9)	21 (7.9)	5 (14.7) ^d	10 (8.1)	2 (13.3)	4 (13.8)
Delivery between ≥24 and <33 weeks	76 (34.5)	36 (14.8) ^c	2 (6.9) ^d	52 (46.0) ^f	3 (23.1)	2 (8.0) ^h
Delivery between ≥24 and <34 weeks	109 (49.5)	51 (20.9) ^c	3 (10.3) ^d	78 (69.0) ^f	6 (46.2)	2 (8.0) ^{h, i}
Pregnancies with no survivors	12 (5.2)	22 (8.3)	6 (17.6) ^d	11 (8.9)	3 (20.0)	5 (17.2)
Pregnancies with 1 survivor	6 (2.6)	9 (3.4)	28 (82.4) ^{d, e}	7 (5.7)	0 (0.0)	24 (82.8) ^{h, i}
Pregnancies with 2 survivors	11 (4.8)	234 (88.3) ^c	_	15 (12.2) ^f	12 (80.0) ^g	_
Pregnancies with 3 survivors	200 (87.3)	_	-	90 (73.2) ^f	-	-
Pregnancies with at least 1 survivor	217 (94.8)	243 (91.7)	28 (82.4) ^d	112 (91.1)	12 (80.0)	24 (82.8)

Values represent medians (range) or n (%). Comparisons are by Mann-Whitney U test for continuous variables and by χ^2 or Fisher's exact test for categorical variables. Excluding pregnancies with delivery <24 weeks. Bonferroni correction with adjusted p value of <0.025. Expectant vs. ER to 2 fetuses. ER to 1 fetus. ER to 2 fetuses vs. ER to 1 fetus. ER to 1 fetus. ER to 2 fetuses vs. ER to 1 fetus. ER to 2 fetuses vs. ER to 1 fetus.

Methods

This was a retrospective study of triplet pregnancies referred to our fetal medicine unit for counseling and further management between 1986 and 2013. In all cases included in the study, ultrasound examination was carried out at 10-14 weeks' gestation to demonstrate 3 live fetuses, determine chorionicity from examination of the intertriplet membranes [4] and calculate gestational age from the crown-rump length of the biggest fetus [5]. Parents were counseled regarding the options of expectant management or ER. All ERs were performed transabdominally by ultrasound-guided intrathoracic potassium chloride injection using a 20-gauge needle. In DCT pregnancies with ER to 1 fetus, both fetuses in the monochorionic pair were reduced. Maternal demographic characteristics, ultrasound findings and (in those undergoing ER) procedure details were recorded in a database. Pregnancy outcomes were collected into the same database when they became available from the referring hospitals, general practitioners or the patients themselves.

The data were combined with the results of previous studies that used similar entry criteria and outcome measures. Essentially, searches of PubMed and Medline (August 2013) were performed to identify all studies meeting the following criteria: triamniotic triplet pregnancies of known chorionicity and with 3 live fetuses at 8–14 weeks' gestation, ER by ultrasound-guided intrathoracic potassium chloride injection, comparison of data on expectant management versus ER over the same study period and the same gestational age at recruitment, and outcomes of miscarriage before 24 weeks' gestation and/or early preterm birth between 24 and 32 or 33 completed weeks.

Statistical Analysis

In TCT and DCT pregnancies managed expectantly or by ER, the rates of miscarriage and early preterm birth were calculated. χ^2 , Fisher's exact and Mann-Whitney U tests were used as appropriate to examine the significance of the differences between the various groups for pregnancy outcomes. In the combined data from our centre and previous reports, 2 × 2 tables for the outcomes of interest were constructed and relative risks, 95% CIs and number needed to treat or harm were calculated when the relative risks did not cross 1.0.

The statistical software package SPSS 20.0 (IBM SPSS Statistics for Windows, Version 20.0; IBM, Armonk, N.Y., USA) and Medcalc (Medcalc Software, Mariakerke, Belgium) were used for all data analyses.

Results

Our Data

In our centre we examined 528 TCT and 167 DCT pregnancies with 3 live fetuses at 10–14 weeks' gestation. The pregnancies were managed expectantly or by ER to 2 fetuses or 1 fetus on the basis of parental choice. In those undergoing ER, this was carried out within 3 days of the initial assessment. The characteristics of the pregnancies and pregnancy outcomes are given in table 1.

The gestational age distribution at delivery of triplet pregnancies managed expectantly and those with ER is shown in figure 1. Survival curves for gestational age at delivery between triplet pregnancies managed expectantly versus those with ER are illustrated in figure 2. There were significant differences between the curves for both TCT ($\chi^2 = 101.536$, d.f. = 2, p < 0.0001) and DCT ($\chi^2 = 37.674$, d.f. = 2, p < 0.0001) pregnancies.

In TCT pregnancies managed expectantly, the rates of miscarriage and early preterm birth before 33 weeks' gestation were 3.9 and 34.5%, respectively. The rate of miscarriage was higher and early preterm birth was lower in TCTs with ER to 2 fetuses (7.9 and 14.8%, respectively) and TCTs with ER to 1 fetus (14.7 and 6.9%). In pregnancies that did not miscarry, the median gestational age at delivery was 34 weeks for the expectant group, 36 weeks for those with ER to 2 fetuses and 38 weeks for those with ER to 1 fetus. The percentage of pregnancies with at least one survivor was 94.8% for the expectant group, 91.7% for those with ER to 2 fetuses and 82.4% for those with ER to 1 fetus.

In DCT pregnancies managed expectantly, the rates of miscarriage and early preterm birth were 8.1 and 46.0%, respectively. This group of DCT pregnancies included 13 in which endoscopic laser surgery was carried out at 16-22 weeks because of severe twin-twin transfusion syndrome. In DCTs with ER to 2 fetuses or ER to 1 fetus, there was a non-significant increase in miscarriage (13.3 and 13.8%, respectively) and decrease in early preterm birth (23.1 and 8.0%, respectively). In pregnancies that did not miscarry, the median gestational age at delivery was 33 weeks for the expectant group, 34 weeks for those with ER to 2 fetuses and 39 weeks for those with ER to 1 fetus. The percentage of pregnancies with at least one survivor was 91.1% for the expectant group, 80.0% for those with ER to 2 fetuses and 82.8% for those with ER to 1 fetus.

In the TCT and DCT pregnancies with miscarriage, the interval between examination or ER and miscarriage is illustrated in figure 3. In the cases of miscarriage, this occurred within 2 weeks of assessment in 1 (5.3%) of the 19 cases in the expectant groups and in 4 (12.5%) of the 32 in the ER groups.

Combined Data

The literature search identified 5 studies fulfilling the entry criteria and the combined data from these studies with ours are shown in table 2 [6–10] and the outcomes are compared in table 3.

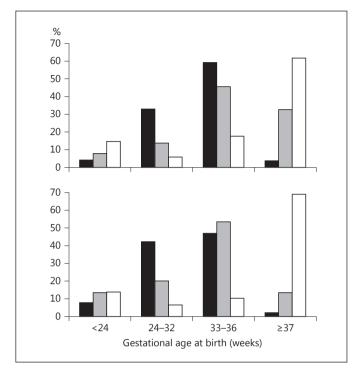


Fig. 1. Gestational age distribution at delivery of TCT (top) and DCT (bottom) pregnancies managed expectantly (black bars) and those reduced to twins (grey bars) or singletons (white bars).

In TCT pregnancies managed expectantly, the rates of miscarriage and preterm birth before 33 weeks were 3.1 and 35.1%, respectively. Compared to the expectantly managed TCTs the rate of miscarriage was higher and early preterm birth was lower in TCTs with ER to 2 fetuses (7.3 and 13.1%, respectively) and TCTs with ER to 1 fetus (11.5 and 8.7%). In DCT pregnancies managed expectantly, the rates of miscarriage and early preterm birth were 8.8 and 46.0%, respectively. In DCTs with ER to 2 fetuses or ER to 1 fetus, there was a non-significant increase in miscarriage (13.3 and 16.7%, respectively) and a decrease in early preterm birth (23.1 and 8%, respectively).

In TCT pregnancies, it was calculated that 5 (95% CI: 4–6) ERs to 2 fetuses need to be performed to prevent 1 early preterm birth, while the number of ERs that will cause 1 miscarriage is 24 (95% CI: 15–70). Similarly, it is necessary to perform 4 (95% CI: 3–6) ERs to 1 fetus to prevent 1 early preterm birth, while the number of reductions that will cause 1 miscarriage is 12 (6–38). In DCT pregnancies, it is necessary to perform 3 (95% CI: 2–5) ERs to 1 fetus to prevent 1 early preterm birth.

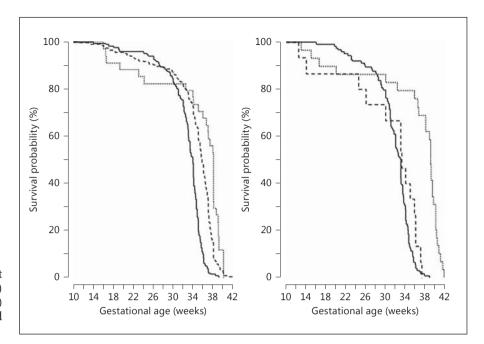


Fig. 2. Survival curve for gestational age at delivery in TCT (left) and DCT (right) pregnancies managed expectantly (——) vs. those with ER to 2 fetuses (---) and reduction to 1 fetus (\cdots) .

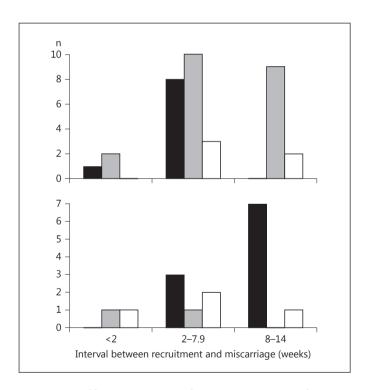


Fig. 3. Interval between gestational age at recruitment and miscarriage in TCT (top) and DCT (bottom) triplet pregnancies managed expectantly (black bars) and those reduced to twins (grey bars) or singletons (white bars).

Discussion

The findings of this study suggest that in TCT pregnancies with 3 live fetuses at 10–14 weeks' gestation the subsequent rates of miscarriage and preterm birth <33 weeks are about 3 and 35%, respectively. In DCT these rates are higher at about 9 and 45%, respectively. In both types of triplets, ER to twins or singletons increases progressively the rate of miscarriage but reduces progressively the rate of preterm birth.

The data from our series are in general agreement with those of previous studies that specified the chorionicity of the triplet pregnancies, recruited cases for the various options at the same gestational age range, and presented outcome data for miscarriage and early preterm birth for the same gestational age cutoffs [6–10]. Studies where there was a difference in gestational age at recruitment between the ER and expectantly managed groups were excluded, as such a difference can influence the apparent rate of pregnancy loss, which is higher with earlier gestational age at recruitment.

In the absence of any randomized trials of ER versus expectant management, the data presented provide the best available evidence for patient counseling and decision-making concerning the preferred option on the management of TCT and DCT pregnancies. A limitation of this and previous studies is the lack of data on rates of death beyond the neonatal period and neurodevelop-

Table 2. Studies reporting on outcome of TCT and DCT pregnancies managed expectantly or with ER to twins or singletons

Management		GA, weeks	n	Miscarriage <24 weeks, % (95% CI)	Preterm birth	
					cutoff, weeks	% (95% CI)
TCT expectant	Antsaklis et al. [6]	8-14	70	2.9 (0.8-9.8)	<33	36.8 (26.3–48.6)
-	Skiadas et al. [7]	11-13	59	0.0 (0.0-6.1)	<34	61.0 (48.3-72.4)
	Present study	10-14	229	3.9 (2.1-7.3)	<33	34.5 (28.6-41.0)
					<34	49.5 (43.0–56.1)
	Total		358	3.1 (1.7-5.4)	<33	35.1 (29.8-40.7)
					<34	52.0 (46.1-57.8)
TCT ER to 2	Antsaklis et al. [6]	8-14	185	8.1 (5.0-12.9)	<33	11.2 (7.3-16.8)
	Athanasiadis et al. [8]	11-13	160	7.5 (4.3–12.7)		
	Skiadas et al. [7]	11-13	87	6.9 (3.2-14.2)	<34	19.8 (12.5-29.7)
	Kuhn-Beck et al. [9]	10-12	136	5.1 (2.5-10.2)	<33	12.4 (7.8–19.2)
	Present study	10-14	265	7.9 (5.2–11.8)	<33	14.8 (10.9–19.7)
					<34	20.9 (16.3–26.4)
	Total		833	7.3 (5.7–9.3)	<33	13.1 (10.5–16.2)
					<34	20.6 (16.6–25.3)
TCT ER to 1	Kuhn-Beck et al. [9]	10-12	44	9.1 (3.6-21.2)	<33	10.0 (4.0-23.1)
	Present study	10-14	34	14.7 (6.4–30.1)	<33	6.9 (1.9-22.0)
					<34	10.3 (3.6–26.4)
	Total		78	11.5 (6.2–20.5)	<33	8.7 (4.0-17.7)
					<34	10.3 (3.6–26.4)
DCT expectant	Skiadas et al. [10]	11-13	13	15.4 (4.3-42.2)	<34	45.5 (21.3-72.0)
	Present study	10-14	123	8.1 (4.5–14.3)	<33	46.0 (37.1–55.2)
					<34	69.0 (60.0–76.8)
	Total		136	8.8 (5.1-14.8)	<33	46.0 (37.1-55.2)
					<34	66.9 (58.3–74.6)
DCT ER to 2	Present study	10-14	15	13.3 (3.7–37.9)	<33	23.1 (8.2-50.3)
					<34	30.8 (12.7–57.6)
DCT ER to 1	Skiadas et al. [10]	11-13	13	23.1 (8.2–50.3)	<34	10.0 (1.8-40.4)
	Present study	10-14	29	13.8 (5.5–30.6)	<33	8.0 (2.2-25.0)
	·				<34	8.0 (2.2–25.0)
	Total		42	16.7 (8.3–30.6)	<33	8.0 (2.2–25.0)
					<34	8.6 (3.0–22.4)

mental impairment in survivors. However, since the risk of infant death and severe handicap are primarily dependent on gestation at delivery, the relative risk of such adverse outcomes for the different management options can be inferred from the proportion of pregnancies delivering at 24–31 weeks.

In TCT pregnancies reduced to twins, compared to those managed expectantly, there is an increase in the rate of miscarriage from about 3 to 7%; with reduction to singletons this rate is further increased to about 12%. The respective rates in each management group in DCT preg-

nancies are about 6% higher than in TCT pregnancies. The higher rate of miscarriage in DCT, compared to TCT pregnancies, is likely to be the consequence of complications arising from intertwin placental vascular communications and/or unequal sharing of the placenta in the monochorionic pair, analogous to that observed in twin pregnancies. In an ultrasound screening study of 365 DCT and 102 monochorionic twin pregnancies with live fetuses at 10–14 weeks, there was spontaneous fetal loss before 24 weeks in about 2 and 12% of cases, respectively [11].

Table 3. Comparison of outcomes of expectant management and ER to twins or singletons in TCT and DCT pregnancies in the combined data of this and previous studies [6–10]

Management	Miscarriage <24 weeks	Preterm birth <33 weeks	Preterm birth <34 weeks
TCT expectant vs. TCT ER to 2			
Proportion comparison	3.1 vs. 7.3%, p = 0.005	35.1 vs. 13.1%, p < 0.0001	52.0 vs. 20.6%, p < 0.000
Relative risk (95% CI)	2.38 (1.27-4.47)	0.37(0.29-0.49)	0.40(0.31-0.50)
NNT/NNH (95% CI)	24 (15-70)	5 (4-6)	3 (3-4)
TCT expectant vs. TCT ER to 1			
Proportion comparison	3.1 vs. 11.5%, p = 0.004	35.1 vs. 8.7%, p < 0.0001	52.0 vs. 10.3%, p < 0.000
Relative risk (95% CI)	3.76 (1.61 – 8.75)	0.25(0.11-0.54)	0.20(0.07-0.58)
NNT/NNH (95% CI)	12 (6-38)	4 (3-6)	2 (2-4)
TCT ER to 2 vs. TCT ER to 1		. ,	•
Proportion comparison	7.3 vs. 11.5%, p = 0.182	13.1 vs. 8.7% , $p = 0.439$	20.6 vs. 10.3%, p = 0.229
Relative risk (95% CI)	1.58 (0.81 – 3.05)	0.67(0.30-1.47)	0.50 (0.17 - 1.50)
NNT/NNH (95% CI)			_ ` ` ′
DCT expectant vs. DCT ER to 2			
Proportion comparison	8.8 vs. 13.3%, p = 0.632	46.0 vs. 23.1%, p = 0.146	66.9 vs. 30.8%, p = 0.015
Relative risk (95% CI)	1.51 (0.37 – 6.12)	0.50 (0.18-1.38)	0.46 (0.20-1.05)
NNT/NNH (95% CI)		_	
DCT expectant vs. DCT ER to 1			
Proportion comparison	8.8 vs. 16.7%, p = 0.160	46.0 vs. 8.0%, p = 0.0002	66.9 vs. 8.6%, p < 0.0001
Relative risk (95% CI)	1.89(0.79-4.49)	0.17 (0.05 – 0.67)	0.13 (0.04-0.38)
NNT/NNH (95% CI)	_	3 (2-5)	2 (1-2)
DCT ER to 1 vs. DC ER to 2		,	,
Proportion comparison	16.7 vs. 13.3%, p > 0.999	8.0 vs. 23.1%, p = 0.315	8.6 vs. 30.8%, p = 0.075
Relative risk (95% CI)	0.80(0.19-3.43)	2.88 (0.55–15.2)	3.59 (0.93 – 13.91)
NNT/NNH (95% CI)			_ ` `
TCT expectant vs. DCT expectant			
Proportion comparison	3.1 vs. 8.8%, p = 0.014	35.1 vs. 46.0%, p = 0.052	52.0 vs. 66.9%, p = 0.006
Relative risk (95% CI)	2.87 (1.30-6.35)	1.31 (1.02–1.69)	1.29 (1.09–1.52)
NNT/NNH (95% CI)	17 (8-73)	9 (5-258)	7 (4–22)

NNT = Number needed to treat; NNH = number needed to harm.

The possible mechanisms leading to miscarriage following ER are (1) procedure-related trauma or infection, in which case the miscarriage would be expected within 2 weeks of ER, and (2) the consequence of the resorbing dead fetoplacental tissue, which could result in miscarriage several weeks or months after ER. Multifetal ER is associated with an increase in maternal serum α-fetoprotein concentration that is proportional to the amount of dead fetoplacental tissue, and this increase persists for several months following the procedure [12]. In our TCT triplets, the rate of miscarriage within 2 weeks of recruitment was 0.44% (1 of 229) in the expectantly managed group and 0.66% (2 of 299) in those with ER to either twins or singletons, suggesting that the direct procedure-related loss from ER may be less than 0.5%. Consequently, most of the excess loss with ER (about 4% for ER to twins and 9% for ER to singletons) is likely to be

due to the presence of dead fetoplacental tissue and is therefore higher with ER to a singleton than to twins.

The beneficial consequence of ER in triplets is the decrease in the rate of early preterm birth. The median gestation at delivery in TCT pregnancies is 34 weeks, and in those reduced to twins and singletons the pregnancy is prolonged to about 36 and 38 weeks, respectively. In TCT pregnancies reduced to twins, compared to those managed expectantly, there is a decrease in the rate of early preterm birth from 35 to 13%, with a potential decrease in the handicap rate to less than half. Reduction to singletons is associated with a further decrease in early preterm birth to about 9% and a decrease in the handicap rate to one fourth. We estimated that to prevent 1 early preterm birth it is necessary to carry out 4 ERs to 2 fetuses or 4 ERs to 1 fetus. In DCT pregnancies reduced to twins, compared to those managed expectantly, there is a decrease in

early preterm birth from 46 to 23%, with a potential halving in the handicap rate. Reduction to singletons is associated with a further decrease in early preterm birth to about 8% and potential decrease in the handicap rate to one sixth. Prevention of 1 early preterm birth can be achieved by carrying out 3 ERs to 1 fetus.

In TCT pregnancies the chance of survival of at least one baby is more than 90% with either expectant management or ER to twins, but the rate is reduced to about 80% with ER to a singleton. In DCT pregnancies, ER to a singleton, compared to expectant management, is associated with a similar, but non-significant, reduction in the

chance of survival of at least one baby. The main difference between expectant management and ER to twins or singletons in both TCT and DCT pregnancies is the higher rate of miscarriage with ER and the higher rate of early preterm birth and potentially higher risk of handicap in survivors with expectant management.

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